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IN THE UNITED STATES DISTRICT COURT  
IN AND FOR THE DISTRICT OF DELAWARE

VANDA PHARMACEUTICALS, INC,	)	
Plaintiff,	)	CIVIL ACTION
v.	)	
	)	NO. 18-651-CFC
	)	
TEVA PHARMACEUTICALS USA,	)	
INC., et al.,	)	
	)	
Defendant.	)	
	)	
	)	
	)	

- - - -  
Wilmington, Delaware  
Thursday, March 31, 2022  
Bench Trial Transcript  
- - - -

BEFORE: HONORABLE COLM F. CONNOLLY, Chief Judge

1 APPEARANCES:

2 SHAW KELLER LLP

3 BY: NATHAN HOESCHEN, ESQ.

JOHN C. ROZENDAAL, ESQ.

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6 For Teva Pharmaceuticals

7  
8 PAUL, WEISS, RIFKIND, WHARTON & GARRISON LLP

9 BY: NICHOLAS GROOMBRIDGE, ESQ.

ERIC STONE, ESQ.

10 JOSEPHINE YOUNG, ESQ.

DANIEL KLEIN, ESQ.

11 -and-

12 MORRIS NICHOLS ARSHT & TUNNELL, LLP

13 BY: KAREN JACOBS, ESQ.

14 For Vanda Pharmaceuticals

15 COZEN O'CONNOR

16 BY: KAUN EKINER, ESQ.

BLAKE COBLENTZ, ESQ.

17 KERRY MCTIGUE, ESQ.

DEREK GRETKOWSKI, ESQ.

18 For Apotex

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CROSS-EXAMINATION- DR. BERGMEIER

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P R O C E E D I N G S

(REPORTER'S NOTE: The following bench trial was held in Courtroom 4B, beginning at 8:30 a.m.)

THE COURT: Good morning. Mr. Rozendaal.

Dr. Bergmeier, you remain under oath.

CROSS-EXAMINATION

BY MR. ROZENDAAL:

Q. Good morning, Dr. Bergmeier.

A. Good morning.

Q. So we left off yesterday starting to talk about the CN268 reference.

Do you recall that?

A. Yes.

Q. So let's go ahead and pull up CN268, which is DTX-301, and let's go to page 301.37.

And what I wanted to confirm was that the CN268 reference describes how to carry out the two process steps that are in Claim 10 of the '465 patent that we have been talking about.

So if we go down at the bottom at Paragraphs 63 and 64, it says synthesis has tasimelteon, right?

A. Yes.

Q. And Paragraph 64 describes adding polypropylene chloride to a methanamine in order to arrive at tasimelteon,

CROSS-EXAMINATION- DR. BERGMEIER

1 right?

2 A. Correct.

3 Q. And we agree that that corresponds to the  
4 propionylating state of the '465 patent, right?

5 A. Yes.

6 Q. And then if we go up before that to see how we got  
7 there, if we go to Paragraphs 61 and 62, it talks about how  
8 to prepare the methanamine that's used to get to the  
9 tasimelteon, right?

10 A. Yes.

11 Q. And it says that you react the carboxamide with a  
12 reducing agent and an acid in order to form the methanamine;  
13 is that fair?

14 A. Yes.

15 Q. And that corresponds to the first of the two process  
16 steps in Claim 10 of the '465, does it not?

17 A. Yes.

18 Q. And just for completeness, in case you're wondering  
19 how we get to the carboxamide, at Paragraphs 59 at the  
20 bottom of Page 36, and 60 at the top of page 37, describe  
21 how to prepare the carboxamide that is used for the  
22 remaining two steps of the reaction; is that right?

23 A. Yes.

24 Q. And people of skill in the art reading these  
25 instructions would know how to carry out those steps, right?

CROSS-EXAMINATION- DR. BERGMEIER

1 A. Yes.

2 Q. Okay. So that's the '268 patent.

3 Now if we go back for just a moment to the other  
4 Chinese patent application we were talking about, which is  
5 the '019 patent, that's DTX-411. If we go to 411, Page 52,  
6 Paragraph 22 at the top, it says to carry out the step in  
7 this claimed process you start with the carboxamide that is  
8 prepared according to the method in the CN268 that we were  
9 just looking at, right? Patent application, I guess.

10 A. Yes.

11 Q. Okay. So then we have -- and that carboxamide  
12 corresponds to the same carboxamide that's in Claims 1 and  
13 10 of the '465 parent, right?

14 A. Yes.

15 Q. Okay. And then the '019 patent, if we go down to the  
16 bottom of that same page, 52, and over to the top half of  
17 Page 53, it describes Embodiment 1, right. And essentially  
18 it tells you how to carry out reaction steps to turn that  
19 carboxamide into tasimelteon, right?

20 A. Yes.

21 Q. All right. And people of skill in the art would  
22 understand how to follow those instructions to arrive at the  
23 tasimelteon product described there, right?

24 A. Yes.

25 Q. Okay. So if we now go back to the Claim 10 of the

CROSS-EXAMINATION- DR. BERGMEIER

1 '465 patent, if we look at the requirements of this claim,  
2 it has to have a composition comprising tasimelteon, right?

3 A. Yes.

4 Q. And then it has two process steps, right?

5 A. Yes.

6 Q. And those two process steps, we agree, are not  
7 something that Vanda invented?

8 A. Correct.

9 Q. Right. That was an old process.

10 A. Yes.

11 Q. We've just established it was described in the CN268  
12 patent.

13 A. Yes.

14 Q. Right. You told us yesterday it was also described  
15 in the Singh reference.

16 A. Yes.

17 Q. And we know from BMS's process documents that BMS had  
18 the process long ago, right?

19 A. Yes.

20 Q. So whatever is new in this claim it's not those two  
21 process steps.

22 A. Yes.

23 Q. Right. So your view of the claim is that what's new  
24 is the impurities.

25 A. Yes.

CROSS-EXAMINATION- DR. BERGMEIER

1 Q. Right. So your point is not that Vanda came up with  
2 a new process for making tasimelteon, it's that Vanda  
3 identified new impurities in an old process.

4 A. Yes.

5 Q. Okay. And just to be clear, the .15 percent impurity  
6 threshold, that's also not something Vanda came up with,  
7 right; that came from regulatory documents?

8 A. Correct.

9 Q. Okay. Now, if someone wanted to make or use  
10 tasimelteon during the term of the BMS '529 patent, which is  
11 the compound patent, it would have needed to have a license  
12 to the patent in order to use the compound, right?

13 A. I believe so, yes.

14 Q. Okay. And we agree that the '529 patent discloses  
15 tasimelteon compositions for pharmaceutical use, right?

16 A. Yes.

17 Q. Okay. So would a POSA have been motivated to apply  
18 the .15 percent threshold from the ICH Guidelines to the  
19 tasimelteon synthesis in the '529 patent?

20 A. I'm sorry, would a what?

21 Q. Yeah. Would a person of skill in the art --

22 A. Oh, okay.

23 Q. -- been motivated to apply the .15 percent impurity  
24 threshold from the ICH Guidelines to the process in the '529  
25 patent if they wanted to make tasimelteon for pharmaceutical

CROSS-EXAMINATION- DR. BERGMEIER

1 use?

2 A. They would have been motivated to get impurities  
3 below that level.

4 Q. Okay. So that's a yes, they would have used that  
5 guideline together with the process in order to come up with  
6 a significantly pure tasimelteon?

7 A. They would have tried to have done that.

8 Q. Okay. And the same thing is true of the process  
9 described in the '268 patent, right? Someone trying to make  
10 tasimelteon according to the '268 patent would be motivated  
11 to apply the impurity thresholds from the ICH Guidelines in  
12 order to come up with a sufficiently pure product, right?

13 A. Yes, but they may not be successful.

14 Q. Right. But they would want to try.

15 A. Yes.

16 Q. Okay. Now, I'd like to talk to you about some of the  
17 assumptions that you relied on in forming your opinions on  
18 validity.

19 So one of the premises of your validity opinions  
20 is that a person of ordinary skill in the art would not have  
21 known or been aware of regulatory considerations concerning  
22 pharmaceutical products. Fair?

23 A. They would not need to know that, no.

24 Q. Well, and they -- so they might not know that.

25 A. They might not.



CROSS-EXAMINATION- DR. BERGMEIER

1 Q. In fact, they would not, right? They don't have to.

2 A. It's not a requirement.

3 Q. Okay. And more specifically, a premise of your  
4 opinions is that a person having ordinary skill in the art  
5 would not have been aware of or understood the teachings of  
6 the ICHQ3A Guidelines.

7 A. They would not need to.

8 Q. Well, and they would not, in your opinion.

9 A. Again, they wouldn't have to. They could. It's  
10 certainly not a disqualification -- you wouldn't take that  
11 person and fire them because they learned that.

12 Q. I see. But in order to be a person of skill in the  
13 art, in your opinion, you don't need to know about the  
14 ICHQ3A Guideline.

15 A. You don't have to, no.

16 Q. All right. Now, you're aware, are you not, Doctor,  
17 that a person of skill in the art is presumed to be aware of  
18 all pertinent prior art?

19 A. Yes.

20 Q. And so you don't think that the ICHQ3A Guideline is  
21 pertinent prior art to the subject matter of the '465?

22 A. I don't think it's a requirement that you know that  
23 particular piece of information. It's something that could  
24 be looked up once you start on your -- trying to purify your  
25 product.

CROSS-EXAMINATION- DR. BERGMEIER

1 Q. We agree that the subject matter, the title of the  
2 '465 patent, is highly purified pharmaceutical-grade  
3 tasimelteon, right?

4 A. Yes.

5 Q. And so just to be clear, even though the subject  
6 matter of the patent is pharmaceutical-grade tasimelteon,  
7 your opinion is that a person of skill in the art does not  
8 need to know about regulatory guidelines for  
9 pharmaceutical-grade products.

10 A. I don't believe they have to know that, no.

11 Q. Okay. Now, you personally don't have any experience  
12 in obtaining FDA approval of a drug product, correct?

13 A. No, I don't.

14 Q. And you don't consider yourself to be an expert in  
15 FDA regulations or approval, right?

16 A. No.

17 Q. You have not been part of a team that has developed a  
18 drug product, right?

19 A. Not all the way to a drug, no.

20 Q. Okay. And, in fact, you, yourself, were not aware of  
21 the ICHQ3A Guidelines prior to your work in this case; is  
22 that right?

23 A. Correct.

24 Q. All right.

25 MR. ROZENDAAL: Thank you, Dr. Bergmeier.

CROSS-EXAMINATION- DR. BERGMEIER

1 I pass the witness.

2 THE COURT: All right. Redirect?

3 MS. YOUNG: I don't have no further questions,  
4 but I do want to clarify one thing for the record because I  
5 think I misspoke when I tried to enter one of the exhibits  
6 yesterday.

7 I would like to offer PTX-829 and 830, which are  
8 both responses to office actions.

9 MR. ROZENDAAL: No objection, Your Honor.

10 THE COURT: All right. They're admitted.

11 (PTX-829 and PTX-830 admitted into evidence.)

12 THE COURT: You may step down.

13 (Witness excused.)

14 MR. ROZENDAAL: So, Your Honor, we have a motion  
15 we'd like to raise with the Court, and I'm wondering if  
16 perhaps it would be appropriate to take up at the first  
17 instance at side bar.

18 THE COURT: How many people have to be cleared  
19 before we went to sidebar?

20 MR. ROZENDAAL: Well --

21 THE COURT: All right. We'll do a sidebar.

22 And then so the record reflects, judging -- I  
23 made the decision based on Mr. Rozendaal's facial reaction.

24 (Whereupon, a discussion was held at sidebar as  
25 follows:)

CROSS-EXAMINATION- DR. BERGMEIER

1 THE COURT: Obviously by facial reactions I was  
2 being silly. The courtroom is crowded and now we have a  
3 sidebar of about 20 people, so that's just the nature of the  
4 beast.

5 Go ahead, Mr. Rozendaal.

6 MR. ROZENDAAL: So, Your Honor, the issue is  
7 that on Dr. Bergmeier's direct, the plaintiff put in front  
8 of him a demonstrative that called attention to the Chinese  
9 '019 patent and elicited testimony about prosecution history  
10 involving a patent.

11 THE COURT: Hold on a second.

12 Yes.

13 MR. ROZENDAAL: And on cross-examination,  
14 Dr. Bergmeier confirmed that the '019 patent describes  
15 99.9 percent pure tasimelteon that has fewer than  
16 0.15 percent by way of all of the named impurities in the  
17 claim at issue in the '465 patent. Also confirmed that  
18 people of skill in the art would be able to follow  
19 instructions of the '019 patent in order to make the  
20 product.

21 And so, that means that that constitutes an  
22 admission that the '019 patent is an anticipating reference  
23 for the claim. Now, we did not list the '019 patent in the  
24 pretrial order as an anticipatory reference, but in light of  
25 this rather unexpected testimony that was elicited initially

CROSS-EXAMINATION- DR. BERGMEIER

1 by the plaintiffs and the evidence that was brought in  
2 without any objection by the plaintiff, we think it would be  
3 appropriate to amend the pleadings to conform the pretrial  
4 order to the evidence and allow us to raise that as a ground  
5 of invalidity.

6 MR. GROOMBRIDGE: We don't, surprisingly,  
7 disagree, Your Honor. Had they raised this in a timely  
8 fashion, we would have put on evidence with a host of other  
9 reasons why the process of the '019 patent is not identical  
10 and therefore it would produce different impurities. And  
11 also that there are reasons in that domestic, as I think Dr.  
12 Bergmeier touched on, eluded to at some point to disbelieve  
13 that, in fact, it would produce what it says it would  
14 produce.

15 And had they raised that, that would have been a  
16 primary focus of debate between the two sides for Your  
17 Honor. And so now for them to come in and say the evidence  
18 is closed, we have an invalidity ground that we didn't put  
19 in the pretrial order, we didn't frame up for this and now  
20 the witnesses are gone.

21 I cannot barely conceive of anything that would  
22 be more prejudicial.

23 MR. ROZENDAAL: Your Honor --

24 MR. GROOMBRIDGE: One more thing -- Mr. Stone  
25 mentioned. We're learning of this now. It wasn't raised

CROSS-EXAMINATION- DR. BERGMEIER

1 last night, it wasn't raised at any point.

2 Now, I understand that it's based on the  
3 testimony that Your Honor heard, you know, in the last few  
4 minutes, but all the same, right, you know, this is an issue  
5 that is literally breaking now.

6 THE COURT: Well, I thought it's based on the  
7 testimony we heard yesterday afternoon. I mean, I heard the  
8 testimony. It struck me that he said on the stand that that  
9 patent and the disclosure that tasimelteon could be made  
10 with -- was it 99.9 percent purity was known in the prior  
11 art. That seems to me to mean that necessarily somebody who  
12 made that tasimelteon as of the priority date would have  
13 necessarily met the impurity limitations in the asserted  
14 claim.

15 MR. GROOMBRIDGE: Had this been raised, for  
16 example, as a basis for invalidity, and we had joined --

17 THE COURT: I don't want you to repeat yourself  
18 because I got what you said. The point is, though, you were  
19 the one who adduced this evidence at trial. I don't believe  
20 that this particular Chinese patent, the '019, had been  
21 mentioned at trial until your side adduced it. And having  
22 adduced it, I think Rule 15 talks about liberal pleading  
23 standards and provides at any time, right, the party can  
24 move to amend the pleadings to conform with the evidence.  
25 You adduced the evidence.

CROSS-EXAMINATION- DR. BERGMEIER

1 It was your witness, right?

2 MR. GROOMBRIDGE: He was our witness.

3 THE COURT: And then there was  
4 cross-examination. You could have done redirect, right?

5 MR. GROOMBRIDGE: We could have done, but at  
6 that time there was no --

7 THE COURT: You could have done redirect this  
8 morning.

9 MR. GROOMBRIDGE: Right, but there was no  
10 argument until now.

11 THE COURT: Then maybe since you're not  
12 prejudiced he can be brought back on redirect.

13 MR. GROOMBRIDGE: Maybe we bring him back and  
14 just say --

15 THE COURT: Let's do that.

16 MR. GROOMBRIDGE: Do you have any reason to, you  
17 know, to go through the '019 patent and see what he says  
18 about it?

19 THE COURT: Right. Okay.

20 MR. ROZENDAAL: That's why I wanted to raise it  
21 promptly, Your Honor.

22 THE COURT: Okay. Let's do that.

23 MR. GROOMBRIDGE: And, Your Honor, just so -- is  
24 he sequestered or maybe confer with him, because we have not  
25 previously discussed this.

CROSS-EXAMINATION- DR. BERGMEIER

1 THE COURT: I think the right answer is you just  
2 put him on the stand and we just adduce the evidence. I  
3 think that's the fairest way to do it.

4 MR. GROOMBRIDGE: Thank you.

5 THE COURT: All right.

6 (Whereupon, the discussion held at sidebar  
7 concluded.)

8 THE COURT: Go ahead.

9 MR. GROOMBRIDGE: Just given the nature of the  
10 situation, I was wondering if we might have a couple of  
11 minutes just to confer about questions that we should ask.

12 THE COURT: Sure. How much --

13 MR. GROOMBRIDGE: Five minutes, maybe.

14 THE COURT: We'll come back at 9 o'clock.

15 (Break taken.)

16 THE COURT: Let's proceed.

17 MS. YOUNG: I'd like to call Dr. Bergmeier back  
18 to the stand.

19 BY MS. YOUNG:

20 Q. Hi, Dr. Bergmeier.

21 A. Hello.

22 Q. Do you recall being asked by Mr. Rozendaal about CN  
23 '019, which I believe is DTX-411?

24 A. Yes, I do.

25 MS. YOUNG: And if you could go to Page 52 and



CROSS-EXAMINATION- DR. BERGMEIER

1 53 and pull up Paragraphs 32 through 34.

2 MR. ROZENDAAL: I apologize. May the witness be  
3 admonished that he's still under oath?

4 THE COURT: You are still under oath.

5 THE WITNESS: Yes.

6 BY MS. YOUNG:

7 Q. Dr. Bergmeier, do you recall Mr. Rozendaal asking you  
8 about this embodiment in CN '019?

9 A. Yes, I do.

10 Q. How is this process here different than what is  
11 disclosed in Claim 10 of the '465?

12 A. They're using a -- well, they are using sodium  
13 borohydride as the reducing agent and I don't believe that  
14 they are adding an acid at the end.

15 Q. Does Claim 10 of the '465 patent require the use of  
16 sodium borohydride?

17 A. No, it does not.

18 Q. So with respect to Claim 10 of the '465 patent, how  
19 was this process different than what is set forth in Claim  
20 10 of the '465?

21 THE COURT: I think the first question is: Is  
22 it different? There's no objection, but it's a bench trial.

23 The first question is: Is it different?

24 THE WITNESS: It is a different procedure that  
25 is spelled out in the specifications for Claim 10.

CROSS-EXAMINATION- DR. BERGMEIER

1 BY MS. YOUNG:

2 Q. How is it different?

3 A. Well, they use a different reducing agent. They use  
4 aluminum hydride and then they add acid at the end of that  
5 procedure. In this one they are using sodium borohydride  
6 and they actually have propionic anhydride acid in there at  
7 the same time to likely generate borane as the ultimate  
8 reducing agent.

9 Q. Based on the process differences between what is set  
10 forth in the '465 patent and what is here disclosed in the  
11 CN019, would one expect to produce different impurities or  
12 have a different impurity profile?

13 A. I would expect there would be some differences in  
14 impurities based on how the process is actually carried out.

15 Q. Let's talk a little bit about the purity of  
16 99.9 percent that's disclosed in the CN019 patent.

17 A. Yes.

18 Q. What is your opinion as to whether or not that figure  
19 is accurate?

20 A. I don't think it's accurate. The melting point is  
21 quite a bit lower. That's usually a pretty decent indicator  
22 of purity. And the optimal rotation that alpha in brackets  
23 there equals the minus 17.3, I believe the one that's  
24 already been reported is somewhere closer to minus 22 or 23.  
25 And so, again, that's an indication that it's probably not

CROSS-EXAMINATION- DR. BERGMEIER

1 as pure as one might really expect for that 99.9 percent  
2 purity.

3 They also really don't give an indication of how  
4 they are determining that purity.

5 Q. Is there any data in CN019 to suggest how that purity  
6 is determined?

7 A. There's actually nothing in here to suggest how that  
8 purity is obtained. Could be an example of an HPLC where  
9 they didn't really look closely for impurities and simply  
10 said 99.9.

11 Q. Is there any HPLC data disclosed in CN019?

12 A. None.

13 Q. Is there anything in CN019 to suggest that they  
14 looked for any impurities 1 through 3, 5 and 6?

15 A. No, there's absolutely nothing in there to suggest  
16 that they looked for impurities. They simply note that they  
17 did chromatographic column, which is pretty standard  
18 purification procedure, but it's not necessarily going to  
19 remove all of the impurities.

20 Q. If they didn't know to look for impurities 1 through  
21 3, 5 or 6, how would one be sure that the tasimelteon was --  
22 had a purity of 99.9 percent?

23 A. You really don't know. You would have to look for  
24 those impurities. You would actually have to carefully  
25 examine your HPLC and, kind of like the FDA responses to

CROSS-EXAMINATION- DR. BERGMEIER

1     Teva and Apotex, check to see if those things can be  
2     detected.

3     Q.     Is it possible that the tasimelteon produced here in  
4     CN019 has more than 0.15 percent of any one of the  
5     impurities 1 through 3, 5 or 6?

6     A.     I think it's very likely.

7             MS. YOUNG: I have no further questions.

8             THE COURT: Just give me a second.

9             There is such a thing in the field, right, of  
10     99.9 percent impurity?

11            THE WITNESS: Yes, there is.

12            THE COURT: And that means the artisans of  
13     ordinary skill, that in the aggregate, the impurities  
14     comprise no more than .01 percent, correct?

15            THE WITNESS: Yes. Yes.

16            THE COURT: All right. Thank you. You may step  
17     down.

18            MR. LUKAS: Good morning, Your Honor.

19     Defendants call Dr. Greenblatt.

20            MR. GROOMBRIDGE: May I proceed, Your Honor.

21            I noticed in the transcript there may be an  
22     error.

23            When Your Honor asked Dr. Bergmeier: "There is  
24     such a thing as 99.9 percent?"

25            He said "Yes."

DIRECT EXAMINATION - DR. GREENBLATT

1 Your Honor then said: "That means in the  
2 aggregate the impurities comprise no more than .01 percent."

3 And I suspect Your Honor meant .1 percent.

4 THE COURT: I don't know whether I misspoke, but  
5 that is certainly what I intended. The problem is the  
6 witness is gone. You know what, he could only have meant  
7 that. We can only agree. It's like a -- yes.

8 MR. GROOMBRIDGE: I think that's pure  
9 arithmetic, Your Honor.

10 THE COURT: It is. Let's clear this up. I  
11 mean --

12 MR. STONE: I can run out and ask him if his  
13 answer would have been "yes" and represent to the Court if  
14 it would make the Court happy?

15 THE COURT: You know what, I don't think it  
16 matters. It's my opinion, but let's --

17 It's undisputed, I think now, that an artisan of  
18 ordinary skill believes that there's such a thing as  
19 99.9 percent purity, right?

20 MR. ROZENDAAL: Yes, Your Honor.

21 THE COURT: Okay. And, therefore, even without  
22 expert testimony, it seems to me I can conclude that in the  
23 aggregate all impurities must be no more than .1 percent.

24 That we can all agree on?

25 MR. ROZENDAAL: Defendants certainly agree with

DIRECT EXAMINATION - DR. GREENBLATT

1       that.

2                   THE COURT: I know that, right.

3                   MR. GROOMBRIDGE: We think that's just  
4       arithmetic, Your Honor.

5                   THE COURT: Yeah, and I don't know why maybe  
6       it's -- I'm brain tired but I must have said .01. My bad.

7                   All right, thank you.

8                                   DIRECT EXAMINATION

9       BY MR. LUKAS:

10      Q.       Good morning, Dr. Greenblatt.

11      A.       Good morning, sir.

12      Q.       Could you please state your full name for the record?

13      A.       David J. Greenblatt, MD.

14      Q.       And did you prepare some demonstratives to assist  
15      with your testimony this morning, Dr. Greenblatt?

16      A.       Yes.

17                   MR. LUKAS: Mr. Brooks, if we could please bring  
18      up DDX-6.1.

19      BY MR. LUKAS:

20      Q.       Dr. Greenblatt, what's your current occupation?

21      A.       I'm a physician and occupied full time at Tufts  
22      University School of Medicine where I'm a professor.

23      Q.       And before we get to your opinions, Dr. Greenblatt,  
24      I'd like to turn your attention in your binder to DTX-398.

25                   Do you see that?

DIRECT EXAMINATION - DR. GREENBLATT

1 A. Yes.

2 Q. And what is that document?

3 A. That is my CV.

4 MR. LUKAS: Defendants move for DTX-398 to be  
5 admitted into evidence, Your Honor.

6 MR. STONE: No objection, Your Honor.

7 THE COURT: All right. It's admitted.

8 (DTX-398 admitted into evidence.)

9 BY MR. LUKAS:

10 Q. If we bring up DTX-398, if you could please briefly  
11 go through your education and work experience,  
12 Dr. Greenblatt.

13 A. Yeah. So 1966 graduated from Amherst College. 1970,  
14 Harvard Medical School. And then from '70 to '72, I trained  
15 in internal medicine, one year at the Montefiore Hospital in  
16 the Bronx and one year on the Harvard Medical Service at  
17 Boston City Hospital which is now Boston Medical Center.

18 Then in '72 to '74, I served a two-year  
19 fellowship in clinical pharmacology at Mass General Hospital  
20 and Harvard Medical School.

21 Q. Dr. Greenblatt, what is pharmacology?

22 A. Pharmacology is the study of the effects of drugs in  
23 living organisms, what their mechanisms of action are, what  
24 their adverse reactions and toxicities are.

25 Clinical pharmacology is how that relates to

DIRECT EXAMINATION - DR. GREENBLATT

1 drugs in humans, specifically.

2 Q. And how long have you been practicing clinical  
3 pharmacology?

4 A. Well, over 50 years.

5 Q. Turning to DDX-6.2, Dr. Greenblatt, have you served  
6 in any leadership positions?

7 A. Yes. One moment, please.

8 Q. And now it's up on the screen for you.

9 A. Okay.

10 Q. DDX-6.12.

11 A. Yeah. So I'm currently the editor of a biomedical  
12 journal called Clinical Pharmacology in Drug Development.  
13 I'm the editor-in-chief. I served for 40 years as  
14 coeditor-in-chief on another journal called the Journal of  
15 Clinical Psychopharmacology, and I'm a member of a number of  
16 editorial boards of other journals.

17 I'm a member of a number of scientific societies  
18 and have served as president of the American College of  
19 Clinical Pharmacology.

20 Q. Have you also published extensively in the field?

21 A. Yes. I have publications, I think, numbering close  
22 to 1,100 as indexed on the National Library of Medicine, and  
23 about 780 of those are original research publications.

24 Q. Turning to DDX-6.3 on the screen, Dr. Greenblatt,  
25 have you received any awards for your research?



DIRECT EXAMINATION - DR. GREENBLATT

1 A. Yes, I have received some awards. The most recent is  
2 the Oscar B. Hunter award in therapeutics, which is awarded  
3 to individuals for lifetime achievement in pharmacology and  
4 therapeutics.

5 MR. LUKAS: Your Honor, defendants would offer  
6 Dr. Greenblatt as an expert in the field of clinical  
7 pharmacology which includes drug metabolism and drug  
8 interactions.

9 MR. STONE: We had stipulated not to object, but  
10 I certainly have no objection, Your Honor.

11 THE COURT: All right.

12 BY MR. LUKAS:

13 Q. Turning to DDX-6.4, Dr. Greenblatt, can you please  
14 briefly outline to the Court what you plan to discuss this  
15 morning.

16 A. Yes. To discuss the particular patents and what the  
17 issues are, what the level of ordinary in the skill in the  
18 art would be in this context. Then some background about  
19 drug metabolism, drug interactions, and pharmacokinetics,  
20 and then the obviousness analysis.

21 Q. If we turn to DDX-6.5, Doctor, can you briefly  
22 summarize the two patents that you were asked to analyze in  
23 this case?

24 A. Yes. Just to summarize, so '829 is about, um, strong  
25 CYP1A2 inhibitor and its potential interaction or action,

DIRECT EXAMINATION - DR. GREENBLATT

1 interaction with tasimelteon.

2 The '910 patent looks at interaction with  
3 tasimelteon by rifampin, which is an inducer of CYP3A and  
4 what that means for --

5 Q. All right. And if we turn to DDX-6.6, Doctor, did  
6 you have any opinions on what the level of what ordinary  
7 skill in the art is as it relates to those two patents?

8 A. Yes. I think the person of ordinary skill would be a  
9 member of a team who would work together with others. But  
10 in my context, it would be expertise in clinical  
11 pharmacology, drug metabolism, pharmacokinetics, and drug  
12 interactions.

13 Q. And in your experience as a clinical pharmacologist,  
14 have you worked as a member of any teams on drug  
15 development?

16 A. Yes, I have.

17 Q. Are there any drugs in particular you have worked on?

18 A. Yes. I have worked, for example, on ramelteon,  
19 Rozerem.

20 Going back to the '70s, I've worked on a number  
21 of benzodiazapine derivatives, such as lorazepam, which is  
22 Ativan, alprazolam, which is Xanax, midazolam which is -- I  
23 forget the name, but those are all drugs used in psychiatry.

24 Then we've been involved in some antidepressant  
25 development and more recently, we've been involved in the

DIRECT EXAMINATION - DR. GREENBLATT

1 development of zolpidem, which is Ambien, the sleep  
2 medication.

3 So I have been involved in team activities like  
4 this for a number of years.

5 Q. All right. Turning to DDX-6.7, Dr. Greenblatt, did  
6 you prepare a demonstrative showing -- outlining what  
7 first-pass metabolism is?

8 A. Yes, I did.

9 Q. Would you please walk the Court through this slide?

10 A. So this is a schematic of what happens when you take  
11 a medication by mouth. And that would be the yellow dot  
12 which then you take the medication and it goes down to the  
13 stomach where it dissolves in fragments and becomes  
14 solubilized. Then the contents of the stomach pass to the  
15 small bowel where most drug absorption happens in the first  
16 couple of feet in the small bowel.

17 There's also a metabolism that happens in the  
18 small bowel lining by an enzyme called CYP3A4, which we'll  
19 talk about.

20 Then after absorption, all of the blood from the  
21 GI tract goes to a specialized circulation called the portal  
22 circulation, and all of that blood empties into the liver  
23 where further metabolism can take place. And, ultimately,  
24 the drug, whatever is remaining, will enter the general  
25 circulation.

DIRECT EXAMINATION - DR. GREENBLATT

1 Q. Are there any enzymes in the liver that are of  
2 particular importance here?

3 A. Yes. There are many drug metabolizing enzymes in the  
4 liver, and the ones we pay most attention to are called the  
5 cytochrome P450 enzymes, abbreviated CYP, and they account  
6 for much of drug metabolism that happens.

7 Q. Turning to DDX-6.8, did you prepare a demonstrative  
8 summarizing or giving an overview of the CYP450 enzymes?

9 A. Yes, I did, and that's on this slide. It shows the  
10 nomenclature. So CYP stands for cytochrome P450, so the  
11 enzymes are named by a number, a letter, and a number.

12 The first number that appears identifies a large  
13 family of enzymes. Then when you add the second letter,  
14 such as A, that narrows it down to a subfamily of a smaller  
15 group of enzymes. And then when you add the third number  
16 and you end up with something like CYP1A2, that identifies  
17 one specific single enzyme.

18 Q. In turning to DDX-6.9, how many specific varieties of  
19 enzymes in the CYP family are important for drug metabolism?

20 A. Well, there are many CYP enzymes, but in the range of  
21 six or eight or maybe a couple more, are the ones that are  
22 most important for drug metabolism. And in the yellow, you  
23 can see six of the named CYP enzymes in the liver that are  
24 named and identified as being most important in drug  
25 metabolism.

DIRECT EXAMINATION - DR. GREENBLATT

1 CYP3A is unique because it's the only one that's  
2 present in the intestines as well as the liver. And CYP3A  
3 is the dominant enzyme in the liver among the CYPs because  
4 it metabolizes 30 to 40 or maybe even 50 percent of drugs  
5 used in clinical practice, either partially or entirely.  
6 And it's also there on the quantitative, most largest  
7 amount.

8 Q. And there's a quote here from DTX-9 which is the  
9 Badyal reference.

10 Do you see that?

11 A. Yes, I do.

12 Q. Did you consider that reference as a background  
13 material in forming your opinions?

14 A. Yes, I did. That's a prior art reference which  
15 basically says what I just said.

16 Q. Right.

17 MR. LUKAS: Defendants would move to have DTX-9  
18 entered into evidence.

19 MR. STONE: No objection.

20 THE COURT: It's admitted.

21 (DTX-9 admitted into evidence.)

22 BY MR. LUKAS:

23 Q. Turning to DDX-6.10, Doctor, how would a person of  
24 ordinary skill in the art go about studying whether a  
25 particular drug interacts with a particular CYP enzyme?

DIRECT EXAMINATION - DR. GREENBLATT

1 A. So the standard process is start with in vitro  
2 models, and this is what the FDA requires before drugs get  
3 to human.

4 So the questions to be answered are up there.  
5 Where metabolism is likely to happen, what metabolites are  
6 formed and how fast, and which specific CYP enzymes are  
7 involved.

8 So that can be done with either, on the left,  
9 homogenates of actual human liver, which are ground up and  
10 the enzymes isolated, or it can be done using individual  
11 enzymes, which are expressed by genetically engineered  
12 microorganisms, and you put them together to get the data  
13 from this model.

14 Q. Okay. And are there any benefits to doing in vitro  
15 testing?

16 A. Yes. You get information that is relevant to drug  
17 metabolism, genetics, drug interactions before you ever get  
18 to humans. So you know what to look for when you come to  
19 human drug development.

20 Q. And does FDA require any of these tests?

21 A. Yes, they do. This process is required by the FDA as  
22 a routine part of drug development.

23 Q. Okay. Turning to -- I'd like you to turn in your  
24 binder --

25 THE COURT: Wait, before you do. So what is a

DIRECT EXAMINATION - DR. GREENBLATT

1 liver microsome?

2 THE WITNESS: Yes. So you get a liver piece  
3 from a human, and those are available from NIH, et cetera,  
4 and you grind it up mechanically, centrifuge it, and you end  
5 up at the bottom with a pellet. And the pellet is what we  
6 call the microsomes, and they are membrane-bound enzymes.  
7 They are not really an entity in the human. They are just  
8 the result of centrifuge. But those microsomes contain the  
9 enzymes on the study in very high density exactly as in the  
10 liver.

11 THE COURT: All right.

12 BY MR. LUKAS:

13 Q. If I could turn with you now to DTX-16 in your  
14 binder, Doctor.

15 A. Yes.

16 Q. Do you recognize this document?

17 A. Yes, I do.

18 Q. And what does this document broadly disclose?

19 A. Yes, it's a general review article about tasimelteon  
20 which appeared in the biomedical literature.

21 Q. And did you consider this document in forming your  
22 opinions?

23 A. Yes, I did.

24 MR. LUKAS: Defendants would have DTX-16 entered  
25 into evidence.

DIRECT EXAMINATION - DR. GREENBLATT

1 MR. STONE: No objection, Your Honor.

2 THE COURT: All right.

3 (DTX-16 admitted into evidence.)

4 BY MR. LUKAS:

5 Q. If we could turn to Page 3 at the bottom of Page 3,  
6 DTX-16 at Column 2.

7 Does DTX-16 disclose anything concerning  
8 pharmacology of tasimelteon?

9 A. Yes, this particular paragraph goes to the mechanism  
10 of action of tasimelteon and other drugs of this class, such  
11 as ramelteon and melatonin. And they act to produce their  
12 pharmacologic effect by binding to these two receptors in  
13 the brain called -- they're called melatonin receptors, MT-1  
14 and MT-2 and the binding affinity numbers. Those are very  
15 small numbers.

16 They are in the so-called picomolar range.  
17 Those are very low concentration numbers and that indicates  
18 very high binding to the target. So this gets at the  
19 molecular mechanism reaction and --

20 THE COURT: How do you spell picomolar for the  
21 Court Reporter?

22 THE WITNESS: P-I-C-O-M-O-L-A-R. It's the next  
23 thing down to nanomolar, which is the next thing down from  
24 micromolar. So it's a factor of --

25 BY MR. LUKAS:



DIRECT EXAMINATION - DR. GREENBLATT

1 Q. Right. I'd like to turn to Page 4 of DTX-16, Column  
2 2.

3 Does Hardeland also disclose what was known  
4 about tasimelteon metabolism at this time?

5 A. Yes, it does.

6 Q. And what does it say about that?

7 A. It's what you see up there, that the drug is  
8 primarily metabolized by CYP1A2, and a couple of other  
9 isoenzymes and then refers back to an earlier study.

10 Q. And is this based on in vitro testing?

11 A. It is, yes.

12 Q. Does Hardeland here cite to another document as  
13 providing a basis for this information?

14 A. Yeah, I've mentioned it's the very last number which  
15 goes back to the Bristol-Myers Squibb publication on this  
16 topic, the scientific publication.

17 Q. Okay. If you could turn in your binder to JTX-35.

18 Do you recognize this document?

19 A. Yes, I do.

20 Q. What is it?

21 A. This is the product label for ramelteon Rozerem.

22 Q. Did you also rely on JTX-35 in your analysis?

23 A. Yes, I did.

24 MR. LUKAS: Defendants would move to have JTX-35  
25 admitted into evidence, Your Honor.

DIRECT EXAMINATION - DR. GREENBLATT

1 MR. STONE: No objection, Your Honor.

2 THE COURT: It's admitted.

3 (JTX-35 admitted into evidence.)

4 BY MR. LUKAS:

5 Q. What is ramelteon, Dr. Greenblatt?

6 A. Ramelteon is a drug closely related to tasimelteon.  
7 It has the same mechanism of action and it's used in  
8 clinical practice to treat sleep disorders.

9 Q. And if we look at the clinical pharmacology a little  
10 bit farther down on Page 1 of JTX-35, what was known about  
11 the pharmacology of ramelteon?

12 A. Very similar to what we saw for tasimelteon. It  
13 binds to the same melatonin receptors with high affinity.  
14 So that's its mechanism of action.

15 Q. Right. And if we turn to Page 3 of JTX-35, was there  
16 anything known about the elimination rate of ramelteon?

17 A. Yes, the mean half-life range of ramelteon was in the  
18 range of 1.1 to 2.6 hours.

19 Q. Okay. If I could turn with you to JTX-93 in your  
20 binder.

21 Do you recognize this document?

22 A. Yes.

23 Q. Did you consider it in forming your opinions?

24 A. I did.

25 MR. LUKAS: Your Honor, we would move to have

DIRECT EXAMINATION - DR. GREENBLATT

1 JTX-93 admitted into evidence.

2 MR. STONE: One moment, Your Honor. I'm sure I  
3 have no objection but he hasn't actually identified the  
4 document.

5 MR. LUKAS: I'm sorry.

6 BY MR. LUKAS:

7 Q. Could you please identify the document, Doctor?

8 A. Yes. It is a review article on ramelteon written by  
9 Dr. Pandi-Perumal appearing in the biomedical literature.

10 MR. LUKAS: Defendants would move to have JTX-93  
11 admitted into evidence.

12 MR. STONE: And I have no objection with that,  
13 Your Honor.

14 THE COURT: All right. It's admitted.

15 (JTX-93 admitted into evidence.)

16 MR. LUKAS: If we could bring JTX-93,  
17 Mr. Brooks.

18 BY MR. LUKAS:

19 Q. Broadly speaking, Doctor, what does this article  
20 disclose?

21 A. Again, it's a general review article about what was  
22 known of ramelteon at the time.

23 Q. Okay. And if we could turn to Page 4 of JTX-93 in  
24 Column 1, second full paragraph.

25 What, if anything, does JTX-93 disclose

DIRECT EXAMINATION - DR. GREENBLATT

1 concerning which enzymes were involved in the metabolism of  
2 ramelteon?

3 A. Yes. It's stating that the principal metabolic  
4 enzymes are CYP1A2 and 2C19 and that drugs that inhibit  
5 those enzymes can increase the levels of the agonist,  
6 meaning ramelteon.

7 Q. Right. And does JTX-93 also disclose metabolism by  
8 CYP3A4?

9 A. Yes, it does.

10 Q. And is this based on -- what type of testing is this  
11 data based on?

12 A. This is based on in vitro models like we discussed  
13 previously.

14 Q. Right. And there's a reference to a Document 16.

15 Do you see that?

16 A. Yes, I do.

17 Q. If we could turn to the references section. And  
18 bring up 16.

19 What is Reference 16, Doctor?

20 A. Reference 16 is a biomedical publication by Dr. Obach  
21 that appeared in Drug Metabolism & Disposition. It's a  
22 study of the metabolism of ramelteon in liver microsomes in  
23 vitro.

24 Q. Do you know Dr. Obach?

25 A. I do.

DIRECT EXAMINATION - DR. GREENBLATT

1 Q. Where does he work?

2 A. He's an employee of Pfizer.

3 Q. Did you consider the Obach reference in forming your  
4 opinions?

5 A. Yes.

6 Q. Turning to DTX-6.11, did you prepare a summary  
7 comparing what was known about the pharmacology of  
8 tasimelteon and ramelteon?

9 A. Yes, so that would be this chart. Looking at  
10 activities the mechanism of action, the half-life insofar  
11 and knowing the structures as the CYP isoforms mostly  
12 involved in metabolism.

13 Q. Right. So let's start first, what was known about  
14 the activity of these two drugs?

15 A. As far as activity goes, they have identical  
16 mechanisms of action. They both bind with high affinity to  
17 the MT-1 and MT-2 receptors. Ramelteon has a short  
18 half-life, at least in animal models at that time,  
19 tasimelteon also had a short half-life.

20 If you look at the structure of the two, they  
21 look very, very close to each other. They're very similar  
22 structures. And when it comes to the enzymes metabolizing  
23 them, in both cases the principal enzyme is CYP1A2. And  
24 there's also a role in CYP3A4 for ramelteon.

25 Q. Right. And I'd like to turn with you to DDX-6.12 and

DIRECT EXAMINATION - DR. GREENBLATT

1 talk a little bit about drug-drug interactions in the  
2 context of metabolism.

3 What is a drug-drug interaction, doctor?

4 A. Well, that -- the situation where two drugs are given  
5 together and one of them alters the metabolism of the other.  
6 So if the -- if the drug causing the interaction is X, which  
7 we sometimes call the perpetrator, modifies the metabolism  
8 of the so-called victim drug or the substrate, that's a drug  
9 interaction.

10 And that can happen in two different directions.  
11 One is if drug X is a CYP inhibitor. That means that X  
12 decreases the activity of the enzymes that metabolize drug  
13 Y. And because the metabolism is slower, the amount of drug  
14 Y in the blood will increase. And you worry about having  
15 levels that are too high and producing toxicity.

16 Induction is the opposite. Drug acts as a  
17 different effect. It does not alter the activity of the  
18 enzymes that are there, but signals the liver to make more  
19 enzyme. So it increases the expression and the amount of  
20 enzymes that metabolize drug Y. That means there are more  
21 metabolism of drug Y, lower concentrations in blood and you  
22 worry about drug ineffectiveness.

23 Q. Is the FDA concerned with drug-drug interactions?

24 A. Yes, absolutely. It's a major consideration when it  
25 comes to evaluating whether a drug should be approved. It's

DIRECT EXAMINATION - DR. GREENBLATT

1 common practice for drugs to be administered together in  
2 clinical medicine.

3 And in order to do that safely and effectively,  
4 the scientific community and treating physicians need to  
5 know about what interactions are possible and what kind of  
6 hazards exist as the result of that. And the information  
7 also needs to be in the product label.

8 Q. Right. I'd like to turn you to DDX-6.13.

9 Were inhibitors and inducers of CYP enzymes  
10 known in the literature?

11 A. Yes, they were well known as of the priority date.  
12 And there were numerous review articles et cetera listing  
13 and talking about various metabolic inducers and inhibitors.  
14 So these are three representative articles in which such  
15 lists are available.

16 Q. Just for the record, DTX-24, which is the 2000 Ogu  
17 reference and the 2001 Badyal reference, DTX-9 and JTX-95  
18 2007 Lynch reference.

19 Did you rely on these as background knowledge?

20 A. Yes, I did.

21 Q. Badyal has already been entered into evidence.

22 Defendants would move to have DTX-24 and JTX-95  
23 admitted into evidence.

24 MR. STONE: No objection, Your Honor.

25 (DTX-24 admitted into evidence.)

DIRECT EXAMINATION - DR. GREENBLATT

1 (JTX-95 admitted into evidence.)

2 BY MR. LUKAS:

3 Q. Was there a strongest known CYP1A2 inhibitor known in  
4 the prior art?

5 A. Yes. The consensus at the time and today is that  
6 fluvoxamine is the strongest possible CYP1A2 inhibitor and,  
7 in fact, it's identified by the FDA and numerous scientific  
8 references as the prototype inhibitor to be used in  
9 experimental studies aimed at that question.

10 Q. Right. And would a person of the ordinary skill of  
11 the art have been aware of a very strong CYP3A4 inducer?

12 A. Yes.

13 Q. And what is that?

14 A. Rifampicin is well known in the prior art and decades  
15 before that to be the strongest possible CYP3A4 inducer  
16 identified as such by the FDA and I think recognized by the  
17 scientific community.

18 Q. Right. Turning to DDX-6.14, was fluvoxamine known to  
19 be an inhibitor of ramelteon?

20 A. Yes, absolutely.

21 Q. And what are we -- and just for the record, before we  
22 get into your opinions.

23 Is this a graph from DTX-28?

24 A. Yes.

25 Q. Which I'll represent for the record is a book chapter



DIRECT EXAMINATION - DR. GREENBLATT

1 from you and a Dr. Van Moltke.

2 Do you recall reviewing that?

3 A. Yes.

4 Q. And you've relied on that as background knowledge?

5 A. Yes.

6 MR. LUKAS: Defendants would move to have DTX-28  
7 admitted.

8 MR. STONE: No objection, Your Honor.

9 THE COURT: All right. It's admitted.

10 (DTX-28 admitted into evidence.)

11 BY MR. LUKAS:

12 Q. What are we looking at here and what is the effective  
13 inhibition of ramelteon, Doctor?

14 A. So this is a graph showing the plasma concentrations.  
15 And you'll notice it's on a logarithmic scale so you can get  
16 the high levels off the graph. Comparing plasma  
17 concentrations when ramelteon alone is given. And that's  
18 the line outlined in purple.

19 Then in the same subjects, when ramelteon is  
20 given together with fluvoxamine, you can see the rising  
21 light blue arrow. And that line at the top of the graph  
22 outlined in light blue is the concentration curve when  
23 ramelteon is given with fluvoxamine. And that's a gigantic  
24 interaction. The extent of exposure to ramelteon is  
25 increased by more than fourfold based on this actual human

DIRECT EXAMINATION - DR. GREENBLATT

1 clinical data.

2 BY MR. LUKAS:

3 Q. I'm sorry, what is -- up here, you have a quote from  
4 JTX-93 --

5 A. Yes.

6 Q. -- at Page 4. What does the Pandi-Perumal reference  
7 say about this interaction?

8 A. That it's a large, huge interaction of more than  
9 100-fold increase of ramelteon on plasma -- concentrations.

10 Q. And I think you mentioned earlier that it was a  
11 fourfold increase. Is it actually more than a 100-fold?

12 A. No, it's more than a 100-fold.

13 Q. In your experience is this a large increase?

14 A. That is a large increase.

15 Q. What -- generally speaking, for a person of ordinary  
16 skill in the art, what would be considered an increase that  
17 would cause concern?

18 A. That depends on what the victim drug is. And for  
19 some drugs, a very small change, like maybe twofold would be  
20 important. For other drugs, maybe not so sensitive.

21 The FDA usual boundary for a large interaction  
22 is fivefold, but this is over a 100-fold. So this is a huge  
23 interaction, clearly significant.

24 Q. Turning to DDX-6.15 with you, Doctor, is this  
25 drug-drug interaction between ramelteon and fluvoxamine

DIRECT EXAMINATION - DR. GREENBLATT

1 reflected in the FDA approved labeling for ramelteon?

2 A. Yes. And the label says don't use them together,  
3 both in a warning and in the drug interaction section.

4 Q. And if we could turn to DDX-6.16.

5 Was ramelteon also known to have a drug-drug  
6 interaction with rifampin?

7 A. Yes, it was.

8 Q. And what are you explaining with this demonstrative,  
9 Doctor?

10 A. So this is from a similar kind of study in which  
11 ramelteon was given alone, that's the top curve. Then when  
12 ramelteon is given with rifampin, which is the CYP3A  
13 inducer, there's a very large decrease in plasma  
14 concentrations, looking at the light blue arrow down to the  
15 lower line there, showing an 80 percent decrease in  
16 ramelteon concentrations, leading to the question of whether  
17 that will reduce or eliminate the efficacy of the drug.

18 Q. And just to be clear, the inhibition of ramelteon by  
19 fluvoxamine and this induction that we're seeing with  
20 rifampin, is this in vitro or in vivo data?

21 A. This is in vivo. This is actual human data.

22 Q. And is this interaction also noted in the label for  
23 ramelteon?

24 A. Yes, it is.

25 Q. And that's -- you have a quote from JTX-35 at

DIRECT EXAMINATION - DR. GREENBLATT

1 Page 10.

2 What does it say about that?

3 A. Results in decreased exposure and efficacy may be  
4 reduced when Rozerem is used with a strong inducer such as  
5 rifampin.

6 Q. Turning to DDX-6.17, did you rely on these three  
7 references --

8 THE COURT: I'm sorry. Could you go back to  
9 that last slide?

10 MR. LUKAS: Sure.

11 THE COURT: Okay. Thank you.

12 BY MR. LUKAS:

13 Q. We see here, again, Doctor, three references: The  
14 DTX-24 Ogu, DTX-9 Badyal, and JTX-95 Lynch.

15 What are these three references saying about  
16 drug-drug interactions and their importance?

17 A. Yes. The message here is that drug interactions were  
18 important, they can alter drug toxicity and efficacy. We  
19 need to know about them through biomedical research so that  
20 we can make coadministration of drugs safer, avoid adverse  
21 reactions, avoid ineffectiveness, and the biomedical  
22 community needs to know about this.

23 Q. Turning to DDX-6.18, in summary, what was known about  
24 the drug-drug interactions for ramelteon?

25 A. Well, basically, in the lower right of the slide,

DIRECT EXAMINATION - DR. GREENBLATT

1 what we just talked about, a huge increase in exposure with  
2 CYP1A2 inhibition, like fluvoxamine, a large decrease in  
3 exposure through CYP3A induction, with rifampin, and when  
4 you fill in the blank as to whether this would be expected  
5 and obvious with tasimelteon, given the similarities in  
6 receptor binding affinity mechanism of action, structure,  
7 and metabolic enzymes involved in metabolism, it would have  
8 been obvious that these interactions are to be expected with  
9 tasimelteon.

10 Q. And if we turn to DDX-6.19, can you please briefly  
11 explain your obviousness analysis for the Court?

12 A. Yes. I believe that a person of ordinary skill in  
13 the art would have found it obvious that the way to avoid an  
14 interaction of tasimelteon and fluvoxamine is to just not  
15 administer the two together. That eliminates the known  
16 hazard.

17 And the same with rifampin. You eliminate the  
18 possibility of an interaction by just not coadministering  
19 them.

20 Q. Okay.

21 MR. LUKAS: And I -- briefly, we looked at  
22 JTX-35 earlier, which was the ramelteon label. I would move  
23 to have that admitted into evidence, Your Honor.

24 MR. STONE: No objection, Your Honor.

25 THE COURT: All right. It's admitted.

DIRECT EXAMINATION - DR. GREENBLATT

1 (JTX-35 admitted into evidence.)

2 BY MR. LUKAS:

3 Q. All right. Turning to DDX-6.21, what aspects of  
4 Claim 13 of the '829 patent were you asked to consider in  
5 your obviousness analysis, which is shown on the right-hand  
6 side of the slide?

7 A. Yeah, the -- the phrases outlined in yellow: Patient  
8 being treated with a strong CYP1A2 inhibitor should  
9 discontinue treatment with that inhibitor before tasimelteon  
10 is given.

11 Q. And in your opinion, what, if any, primary reference  
12 would a person of ordinary skill in the art have relied upon  
13 as teaching or suggesting those claim elements?

14 A. I think that that's -- that is stated in the  
15 Hardeland reference on the left part of the slide.

16 Q. Right. And so you have a quote from DTX-16, the  
17 Hardeland reference, at Page 4.

18 What does that disclose?

19 A. It discloses that CYP1A2 is the principal isoenzyme  
20 responsible for metabolism, and for that reason, even though  
21 at that point we don't have specific warnings or  
22 contraindications for tasimelteon, based on the available  
23 evidence, and in particular this reference, a person of  
24 ordinary skill in the art would have known that these should  
25 be coadministered with caution.

DIRECT EXAMINATION - DR. GREENBLATT

1 Q. And you also quote Page 6 of DTX-16 at the bottom.

2 Do you see that?

3 A. Yes.

4 Q. And what does Hardeland -- or does Hardeland make any  
5 recommendations based on this observation?

6 A. Yes, you proceed with caution.

7 Q. And in your opinion, would a person of ordinary skill  
8 in the art have followed this recommendation?

9 A. Yes, absolutely.

10 Q. And based on following that recommendation, what is  
11 your opinion on the obviousness of Claim 14 of the '829  
12 patent?

13 A. I believe it's obvious.

14 Q. Would a person of ordinary skill in the art require  
15 in vivo data to make this inference?

16 A. It wasn't necessary. You knew enough at the time of  
17 the priority date to understand. It would have been obvious  
18 that this interaction is possible or likely and caution is  
19 needed.

20 Q. Okay. Turning now, Doctor, to DDX-6.23, the '910  
21 patent. What aspects of Claim 4 of the '910 patent were you  
22 asked to consider in your analysis?

23 A. Again, on the right the passages in yellow, the  
24 patient is being treated with rifampin, and the way you  
25 avoid the interaction of tasimelteon with rifampin is to

DIRECT EXAMINATION - DR. GREENBLATT

1     discontinue rifampin treatment before starting  
2     administration of tasimelteon.

3     Q.       And in your opinion, is there a primary prior art  
4     reference that a person of ordinary skill in the art would  
5     have looked to as teaching or suggesting those elements?

6     A.       Yes, that would be this -- the reference Pani-Perumal  
7     in which they identified with ramelteon that CYP3A4  
8     contributes to metabolism, and, therefore, giving an inducer  
9     will increase the amount of CYP enzyme, decrease the levels  
10    of ramelteon, and that combination should be avoided to  
11    avoid a drug interaction.

12    Q.       Right. Now this Pandi-Perumal reference doesn't  
13    disclose tasimelteon, right?

14    A.       Correct.

15    Q.       Is there anything particular about CYP3A4 that led to  
16    your conclusion here?

17    A.       From the background information, we know that CYP3A4  
18    is in the gastrointestinal tract, it's the most abundant in  
19    the liver, that and rifampin is a very strong inhibitor --  
20    inducer of CYP3A4 and can increase the levels of that enzyme  
21    by manyfold.

22    Q.       And in your opinion, would it be necessary to be able  
23    to predict the magnitude of a drug-drug interaction here  
24    between tasimelteon and rifampin for these claim elements to  
25    be obvious?



CROSS-EXAMINATION - DR. GREENBLATT

1 A. No, you don't need to know the quantitative size of  
2 the interaction, only that it is surely to be expected.

3 MR. LUKAS: I will pass the witness.

4 MR. STONE: Your Honor, if I could have one  
5 moment.

6 THE COURT: Sure, no problem.

7 CROSS-EXAMINATION

8 BY MR. STONE:

9 Q. Hello, Dr. Greenblatt. My name is Eric Stone. We  
10 haven't met.

11 A. Yes. Hello, sir.

12 Q. Can we have a bond at the outset, you went to Amherst  
13 College, right?

14 A. Yes.

15 Q. I went to Williams. Can we agree we will do this  
16 anyway?

17 A. Yes, I forgive you for that.

18 Q. And I you.

19 Doctor, you cited a number of references in your  
20 slide deck, and I just want to make sure that I understand  
21 exactly what your obviousness theory is.

22 You differentiated background documents from  
23 what you called the primary references, correct?

24 A. Yes, I did do that.

25 Q. Okay. And the primary reference for Claim 14 of the

CROSS-EXAMINATION - DR. GREENBLATT

1 '829 patent, that's the one that's about CYP1A2, is  
2 Hardeland, correct?

3 A. Yes, that's correct. I mean, my understanding is  
4 that it needs to anchor on a single source.

5 Q. Right. The way the obviousness analysis begins is by  
6 asking, what would a person of ordinary skill at the  
7 priority date --

8 A. Yes.

9 Q. -- knowing what was known have thought when trying to  
10 solve this problem. Correct?

11 A. Yes.

12 Q. And you know you're not allowed to start with what we  
13 now know is the answer and work backwards.

14 A. I understand.

15 Q. You were told that that's what's called hindsight and  
16 you can't do that.

17 A. Correct.

18 Q. And for the CYP3A4 patent, which is Claim 4 of the  
19 '910 patent, your primary reference, you just told us on  
20 your direct, is the Pandi-Perumal reference, correct?

21 A. That is correct, subject to the same, you know,  
22 instruction about the -- how this is all put together.

23 Q. Sure. By way of example, one of the things you told  
24 us at the very end was that it was known that CYP3A4 is a  
25 very common enzyme in the liver, correct?

CROSS-EXAMINATION - DR. GREENBLATT

1 A. Yes.

2 Q. Those words don't need to be in Pandi-Perumal; a  
3 skilled artisan would know that CYP3A4 is a prevalent enzyme  
4 even if that reference never said so. Correct?

5 A. Yes.

6 THE COURT: Can we have sidebar?

7 MR. STONE: Sure.

8 THE COURT: Thank you.

9 (Whereupon, a discussion was held at sidebar as  
10 follows:)

11 THE COURT: Mr. Stone, what's a primary  
12 reference? Under the law, is it a legal term?

13 MR. STONE: It is common in an obviousness  
14 combination to say a person would read this in light of the  
15 teaching of that and in light of the teaching of that other  
16 thing, but the person would start with this document.  
17 That's what a primary reference is.

18 THE COURT: Does it have legal import?

19 MR. STONE: It does in the following sense. You  
20 would ask why the person would ever pick that document up.  
21 For example, if the question is, how do I get from  
22 Wilmington home to New York, and somebody says, it would be  
23 obvious because of the Encyclopedia Britannica of the War of  
24 1812, one might wonder about the starting point.

25 By way of example, Hardeland is a review article

CROSS-EXAMINATION - DR. GREENBLATT

1 of everything known about tasimelteon publically, makes  
2 sense as a place to start if you want to think about, what  
3 do we know about tasimelteon and its metabolism.

4 I think Your Honor is about to hear in the  
5 cross-examination that he told us on direct that the  
6 reference you would start with for the CYP3A4 patent is a  
7 reference that he also testified doesn't even mention  
8 tasimelteon, and we're going to be having a conversation  
9 about how it could possibly be that you would start there.

10 THE COURT: All right. I just want to  
11 understand because I don't recall ever in my own opinions on  
12 obviousness using the term "primary reference" and I just  
13 want to understand.

14 Does it have legal significance in your opinion?

15 MR. STONE: Only insofar as it asked where did  
16 you start, it does not have to have more elements. For  
17 example, than other references do.

18 Although, I think there is sort of a limit to  
19 that if you get one word out of the primary reference and  
20 you get a comma out of the second one, it starts to sound  
21 like hindsight. But there's no particular requirement that  
22 the primary reference had X percentage of the claim or  
23 anything like that, if that's what Your Honor is asking.

24 THE COURT: Well, I'm also asking: Has the  
25 Court defined as a legal matter what the primary reference

CROSS-EXAMINATION - DR. GREENBLATT

1 is?

2 MR. STONE: Mr. Klein is bursting with utterance  
3 and he's closer to this. Would you mind if I called a  
4 friend? I want to make sure I get this right given it's a  
5 question about the law.

6 THE COURT: Actually, I'll tell you what. I'll  
7 briefly let the other side speak, but I know enough now to  
8 let it go. I'm going to let it go anyway. And I'll have  
9 something in my brain about this and then we can sort out  
10 whether there's legal significance to it or -- as opposed to  
11 this is why it would be relevant.

12 In any event, even if the term doesn't have  
13 legal significance, if the witness said in the past  
14 something about a primary reference, it's fair game to  
15 cross-examine him about this.

16 MR. STONE: Thank you, Your Honor.

17 THE COURT: We'll come back to legal  
18 significance.

19 MR. LUKAS: I want to explain, we were required  
20 to narrow our combinations of prior art references for  
21 obviousness in this case. We narrowed it down to what we  
22 thought were the two references that we could use in a  
23 combination. And he provided some background knowledge on  
24 other reference of a person skilled in the art would look at  
25 that primary reference through the lens of. But if you come

CROSS-EXAMINATION - DR. GREENBLATT

1 down to the final combination, Your Honor is going to be  
2 asked to determine whether these patents are obvious. It's  
3 these three references in view of background knowledge of  
4 POSAs is how the law is required under KSR.

5 THE COURT: The bottom line here, I know as a  
6 case management matter or technique, courts say limit  
7 yourself to number of references, but clearly a POSA has  
8 background knowledge.

9 MR. STONE: Of course.

10 MR. LUKAS: Of course.

11 THE COURT: And you can sample it in a single  
12 reference or anything else. It's just a helpful way of  
13 approaching it.

14 MR. STONE: Let me say one more thing if I  
15 could, because I think it will help the Court. These  
16 drug-drug interaction claim elements are in claims that also  
17 talk about administering tasimelteon to treat Non-24. The  
18 defendants', in the plural possessive, combinations also  
19 include references that talk about treating non-24 with  
20 tasimelteon. The Hack reference that we talked about  
21 yesterday I think Lankford. This witness is only talking  
22 about the drug-drug interaction elements of those claims and  
23 I'm asking him what the reference is for those elements. I  
24 just wanted to put that.

25 MR. LUKAS: Right --

CROSS-EXAMINATION - DR. GREENBLATT

1 THE COURT: I get that. That much I did get.

2 MR. STONE: All right.

3 THE COURT: Let me ask you while you're all  
4 here, is Pfizer the owner of one of the parties or something  
5 like that?

6  
7 MR. STONE: No. Your Honor is trying to get why  
8 are we talking about ramelteon. I promise we're going to be  
9 getting there.

10 THE COURT: Yeah, well, he's got something to do  
11 with it, I get that.

12 MR. STONE: Yes.

13 THE COURT: Well, I'll wait, but, thank you.

14 (Whereupon, the discussion held at sidebar  
15 concluded.)

16 BY MR. STONE:

17 Q. Thank you. And let's do a moment of vocabulary for  
18 the court reporter.

19 The name of the reference that we are talking  
20 about is spelled P-A-N-D-I-P-E-R-U-M-A-L, correct, Doctor?

21 A. Yes.

22 Q. And I think each of us is coming close to a consensus  
23 pronunciation but that's the reference that we have in mind;  
24 is that fair?

25 A. Yes.

CROSS-EXAMINATION - DR. GREENBLATT

1 Q. Thank you.

2 Doctor, what's your understanding of what the  
3 priority date is for these patents at which the obviousness  
4 analysis must be conducted?

5 A. My best understanding is late in 2012. I don't  
6 recall the exact month.

7 Q. Late in 2012?

8 A. Yes.

9 Q. And if it turned out that the priority date for the  
10 3A4 patent is a little -- well, it doesn't matter.

11 Withdrawn. We can work with that.

12 In 2012, irrespective of what month it was,  
13 tasimelteon was not approved in the United States, correct?

14 A. Correct.

15 Q. So our hypothetical person of skill asking the  
16 question "How do I administer tasimelteon" is -- it's a  
17 purely, in this case, hypothetical exercise because nobody's  
18 administering tasimelteon as of the prior art date, correct?

19 A. In clinical practice, yes, but it's been administered  
20 plenty in clinical trials.

21 Q. Sure. And I didn't -- that's a very fair point.

22 In terms of a person out there in the community  
23 trying to figure out how to treat a patient with non-24,  
24 that hasn't happened at this point in time, correct?

25 A. In actuality in the United States, that's correct.



CROSS-EXAMINATION - DR. GREENBLATT

1 Q. Okay. With the CYP1A2 patent, the one in which the  
2 interaction is tasimelteon with fluvoxamine or another  
3 CYP1A2 inhibitor, what is the question that you think the  
4 skilled artisan is trying to answer?

5 A. How to avoid the interaction.

6 Q. How to avoid the interaction between what?

7 A. Between tasimelteon and fluvoxamine.

8 Q. Okay. So at that point in time, the skilled artisan  
9 would have to have a reason to think there is an interaction  
10 between tasimelteon and fluvoxamine, correct?

11 A. Correct.

12 Q. Okay. And with respect to the CYP3A4 patent, I take  
13 it, the question the skilled artisan is trying to answer is  
14 how to avoid the interaction between tasimelteon and  
15 rifampicin or another strong CYP3A4 inducer, correct?

16 A. Correct.

17 Q. Which would mean that the skilled artisan would have  
18 to know that there is or at least suspect that there is an  
19 interaction between tasimelteon and rifampicin? It's the  
20 same thing, right?

21 A. Or be unable to exclude it.

22 Q. Well, okay. That's important. And I think I know  
23 why you're giving a different answer for this patent.

24 There are all kinds of CYP1A2 -- withdrawn.

25 CYP, C-Y-P, is the cytochrome P450 class of

CROSS-EXAMINATION - DR. GREENBLATT

1 liver enzymes, correct?

2 A. Yes.

3 Q. They are not exclusively in the liver. Some of them  
4 are in the gut, but they are primarily in the liver,  
5 correct?

6 A. Yes, that's reasonable.

7 Q. Okay. And in terms of what the skilled artisan is  
8 trying to do, the skilled artisan -- withdrawn. I shouldn't  
9 be telling you. I should be asking you.

10 Did they explain to you that in an obvious  
11 analysis -- obviousness analysis, the skilled artisan has to  
12 first have a reason to answer the question, correct?

13 A. Possibly, yeah. I don't explicitly remember.

14 Q. Okay. Maybe we'll come back to that.

15 Let's talk about Hardeland.

16 MR. STONE: Mr. Weir, would you please put up  
17 DTX-16. We'll start at the first page.

18 BY MR. STONE:

19 Q. This is an article published in something called  
20 "Current Opinion in Investigational Drugs." We see that up  
21 in the top right, correct?

22 A. Correct.

23 Q. By a person Rudiger Hardeland?

24 A. Rudiger Hardeland.

25 Q. That's impressive. I will not attempt, if it's okay

CROSS-EXAMINATION - DR. GREENBLATT

1 with you and the Court, to pronounce it in the German.

2 But we can agree that's his name, correct?

3 A. Yes.

4 Q. And the article is entitled "Drug Profile:  
5 Tasimelteon, a melatonin agonist, for the treatment of  
6 insomnia and circadian rhythm sleep disorders."

7 Do you see that there?

8 A. I do see that there, yes.

9 Q. Now, current opinion in investigational drugs is not  
10 a peer-reviewed journal, correct?

11 A. It certainly is.

12 Q. It certainly?

13 A. Is.

14 Q. It is a peer-reviewed journal?

15 A. Yes.

16 Q. Okay. And it is your contention that this is a  
17 reference that a person of ordinary skill would look at --  
18 in fact, it's your primary reference, you've told us, for  
19 the CYP1A2 patent, correct?

20 A. Again, I'm speaking with respect to what I was  
21 advised, which was that a single reference has to be the  
22 anchor for the subsequent analysis. So, yes, this is  
23 identified as the anchor.

24 Q. Okay. I'm perfectly happy to use the word "anchor"  
25 reference if that makes you more comfortable.

CROSS-EXAMINATION - DR. GREENBLATT

1 This is your anchor reference, correct?

2 A. Yes, based on what I just said.

3 Q. Right. And for the CYP1A2 patent, I should have been  
4 more specific, this is your anchor reference, correct?

5 A. Yes.

6 Q. And this is a -- I have the wrong binder, forgive me.

7 If you could turn in your white binder to  
8 DTX-16. And just, you know, turn the pages. This is about  
9 an 8-page single-spaced two-column compilation of what was  
10 known about tasimelteon as of that point; is that fair?

11 A. Yes, based on this particular reviewer's assessment  
12 of what was available, yes.

13 Q. Okay. And you mentioned on your direct examination  
14 that this is a review article, correct?

15 A. Correct.

16 Q. And conceding, as I must, that Amherst is a college,  
17 when you were in college you learned the difference between  
18 a primary source and a secondary source, correct?

19 A. Yes. And we teach that to medical students now.

20 Q. And this is a secondary source, correct?

21 A. Right, it's not a primary source.

22 Q. Let's talk about the paragraph that you talked about  
23 in your direct examination.

24 MR. STONE: Mr. Weir, could you bring up  
25 DTX-16.4.

CROSS-EXAMINATION - DR. GREENBLATT

1 BY MR. STONE:

2 Q. And why don't we zoom in right down here in the  
3 bottom -- actually, before we do that.

4 Dr. Greenblatt, do you see that in the bottom  
5 left, I'm going to be taking you to a paragraph that is in a  
6 section called "Metabolism and Pharmacokinetics"?

7 A. Yes.

8 Q. Okay. And so if a person of skill reading Hardeland  
9 for a review of what was known at the time about tasimelteon  
10 wanted to learn about metabolism, that might be a good place  
11 to look, the metabolism section.

12 Agreed?

13 A. Yes, certainly.

14 Q. And then in the --

15 MR. STONE: Mr. Weir, if you could zoom in on  
16 where I am showing you, thank you.

17 BY MR. STONE:

18 Q. We looked at this on the direct examination, although  
19 you highlighted only some of the words and I want to spend a  
20 minute with you on it.

21 It says: A study using microsomes that  
22 overexpress specific CYP exoenzymes.

23 We're going to pause there for some vocabulary.

24 The study in question is the one that you  
25 mentioned on your direct examination is from BMS, correct?

CROSS-EXAMINATION - DR. GREENBLATT

1 A. Yes.

2 Q. Okay. And we will come to that study in a moment and  
3 when I put it up, I'll spell the name for the court  
4 reporter, but we will come to it in a moment.

5 Microsomes that overexpress specific CYP  
6 exoenzymes, what that means is that in each of these cell  
7 lines in which the test is being done, the cells have been,  
8 to oversimplified, programmed to create more of these CYP  
9 enzymes than would be found ordinarily.

10 That's what "overexpress" means?

11 A. No, it's -- and I speak from having done this myself.

12 Q. Sure.

13 A. Okay. So basically the microorganisms, which are not  
14 liver cells --

15 Q. Understood.

16 A. -- they are programmed by genetic techniques by  
17 transfection by DNA so that those cells get the instruction  
18 to make only one enzyme. So that's what "overexpress"  
19 means. It doesn't mean that it makes large amounts of that  
20 enzyme because the cell is not -- it's not a liver cell. It  
21 doesn't normally make enzymes.

22 But what it does do is make only one enzyme so  
23 that you're able to take the microsomes, that pellet that we  
24 talked about, from that microorganism and study only 1A2.  
25 The amounts there are very small, as it turns out, but the

CROSS-EXAMINATION - DR. GREENBLATT

1 advantage is that it's only 1A2.

2 Q. Okay. We're going to come back to that.

3 Let's talk about what it found in these cells  
4 that have been recombinantly transfected to produce the  
5 enzymes.

6 The study to which Hardeland is referring  
7 suggested that tasimelteon was primarily metabolized by the  
8 CYP1A2, 1A1, 2D6 and 2C9 isoenzymes. Let's stop there for a  
9 moment. We'll keep going.

10 You highlighted that part in your direct,  
11 correct?

12 A. That's correct.

13 Q. And the very first enzyme, among that group of four,  
14 is CYP1A2, correct?

15 A. Correct.

16 Q. So if a person of ordinary skill reading the  
17 Hardeland reference wanted to know, at least in this assay,  
18 which enzymes were shown to metabolize tasimelteon, she  
19 would see that it was shown to be metabolized primarily by  
20 four enzymes, one of which is CYP1A2, correct?

21 A. That's what it says here, but I think a person who  
22 wanted the rest of the information would go back to the  
23 original data.

24 Q. Interesting. We're going to do that, too, but let me  
25 just finish with this paragraph.

CROSS-EXAMINATION - DR. GREENBLATT

1                   What the rest of the sentence says, was: You  
2 agree that in the verb "largely unaffected" the subject is  
3 still tasimelteon?

4           A.       Yes.

5           Q.       Okay. But that tasimelteon was largely unaffected  
6 by, and we see three, four, five, six enzymes, one of which  
7 is CYP3A4, the last one, correct?

8           A.       That's correct.

9           Q.       And the only thing -- now, you also told us on your  
10 direct examination that Hardeland specifically warns or  
11 cautions, at least, about coadministration with some CYP1A2  
12 enzymes, correct?

13          A.       Coadministration of --

14          Q.       Of tasimelteon.

15          A.       With inhibitors?

16          Q.       You are absolutely right. I misspoke. Withdrawn.

17                   And you told us on your direct examination that  
18 Hardeland explicitly cautions about administration of  
19 tasimelteon with certain enzyme inhibitors, correct?

20          A.       Yes, particularly 1A2 inhibitors.

21          Q.       Particularly 1A2 inhibitors.

22                   I want you to put a pin in something in your  
23 head if you can. This paragraph tells the reader that a  
24 study using microsomes found that tasimelteon was primarily  
25 metabolized by the CYP1A2, 1A1, 2D6 and 2C9 enzymes, but was



CROSS-EXAMINATION - DR. GREENBLATT

1 largely unaffected by a number of enzymes, including 3A4,  
2 the enzyme in one of our patents.

3 That's what it says, correct?

4 A. That's what it says, but you left out a word, the  
5 microsomes that overexpress specific CYP. That's not the  
6 same as microsomes.

7 Q. Dr. Greenblatt, I understand that you couldn't join  
8 us in the city -- in Wilmington until yesterday, and that's  
9 why we waited until this morning. It's possible that they  
10 didn't tell you this so I hope you'll let me. We're on the  
11 clock. If you wouldn't mind me answering my questions, they  
12 can ask you whatever they would like to in redirect. But  
13 I'd like to see if you can give me an answer to my  
14 questions.

15 Is that fair?

16 A. Yes, sir, I will try.

17 Q. And the thing I'd like you to put a pin in is the  
18 sentence "largely unaffected 3A4 isoenzyme."

19 Do you see that?

20 A. I see that, yes.

21 Q. Let's now turn to DTX-16.6. We're staying in the  
22 same exhibit, we're turning to Page 6. We're looking at the  
23 section that says: Side Effects and Contraindications. If  
24 a skilled artisan wanted to know about possible  
25 contraindications from what was known about tasimelteon,

CROSS-EXAMINATION - DR. GREENBLATT

1 this seems like a good place to look, right?

2 A. Let me look. Yes.

3 Q. Okay. And there is a paragraph. --

4 MR. STONE: The second paragraph, Mr. Weir, just  
5 bring up the first half of it.

6 BY MR. STONE:

7 Q. What Hardeland tells our skilled -- person of  
8 ordinary skill is: No detailed lists of contraindications  
9 have been provided, but these may be deduced from general  
10 experience.

11 Do you see that?

12 A. Yes, I do.

13 Q. Evidential hypersensitivity, relationship to CYP  
14 metabolism and known melatonergic actions.

15 Do you see that there?

16 A. Yes.

17 Q. As tasimelteon is metabolized by the CYP enzymes 1A2,  
18 1A1, 2D6 and 2C9, again citing the BMS reference to which  
19 we'll turn. Coadministration of any drug that inhibits one  
20 of these exoenzymes should be regarded with caution,  
21 correct?

22 A. That's what it says, yes.

23 Q. So the rest of the examination we're going to agree  
24 on something. Hardeland says coadministration should be  
25 regarded with caution with respect to CYP1A2. And I'll talk

CROSS-EXAMINATION - DR. GREENBLATT

1 to you about what impact that should have on a person with  
2 ordinary skill. But Hardeland does not say coadministration  
3 should be regarded with caution with respect to 3A4,  
4 correct?

5 A. That does not appear in this statement, you are  
6 right.

7 Q. Well, okay. I don't want to fence with you. It  
8 doesn't appear anywhere in the article. Hardeland never  
9 says "Regard administration of tasimelteon with CYP3A4 with  
10 caution," correct?

11 A. As far as I know, yes.

12 Q. Well, you've read it many times. Let's see if we can  
13 get there.

14 Sir, it doesn't say that, right?

15 A. I will take what you say as correct.

16 Q. And the other reference, Pandi-Perunal, that we're  
17 going to come to, doesn't mention a single word about  
18 tasimelteon metabolism, correct?

19 A. We would have to look at the reference. I think it  
20 was mostly about ramelteon.

21 Q. Okay. Other than one sentence that refers to the  
22 existence of tasimelteon, all of Pandi-Perunal is about  
23 ramelteon, correct?

24 A. I will take what you say as correct.

25 Q. Okay.

CROSS-EXAMINATION - DR. GREENBLATT

1 Now, let's go back -- don't need to go back.

2 I'll just remind you.

3 What the Hardeland reference said with respect  
4 to 3A4 was that tasimelteon was, quote, largely unaffected  
5 by 3A4, correct?

6 A. Those are the words, yes.

7 Q. Yes. Let's go look at Vachharajani,  
8 V-a-c-h-h-a-r-a-j-a-n-i, which is the BMS paper that  
9 Hardeland is citing, okay?

10 A. Yes.

11 Q. Rather than making you look at the bibliography,  
12 would you agree with me that Vachharajani is, in fact, the  
13 reference that Hardeland is citing?

14 A. Correct.

15 Q. All right. Turning in your binder to JTX-91.

16 Are you there?

17 A. I am, yes.

18 Q. Do you recognize that to be the Vachharajani  
19 reference?

20 A. I do.

21 MR. STONE: I offer JTX-91.

22 MR. LUKAS: No objection.

23 THE COURT: All right. It's admitted.

24 (JTX-91 admitted into evidence.)

25 MR. STONE: Mr. Weir, let's pull up the top part

CROSS-EXAMINATION - DR. GREENBLATT

1 of Vachharajani.

2 BY MR. STONE:

3 Q. The title of this article is "Preclinical  
4 Pharmacokinetics and Metabolism of BMS-214778, a Novel  
5 Melatonin Receptor Agonist."

6 Do you see that there?

7 A. I do.

8 Q. All right. And the three authors of the article are  
9 disclosed for Bristol-Myers Squibb, correct?

10 A. Correct.

11 Q. Which you know developed tasimelteon, right?

12 A. Yes.

13 Q. Now, a person having ordinary skill in the art, I  
14 think you told us would -- well, withdrawn. I'll just ask.

15 Would your hypothetical person of ordinary skill  
16 read Vachharajani or would they just stop with Hardeland?

17 A. I think they would gather as much information as  
18 possible which would mean going back to primary literature  
19 that's directly pertinent.

20 Q. In fact, at one point in time, Vachharajani was  
21 initially one of the main documents you relied on in forming  
22 your opinions about the obviousness of the patents in this  
23 case, correct?

24 A. Yes, I did rely on that.

25 Q. In fact, at your deposition you told us it was one of

CROSS-EXAMINATION - DR. GREENBLATT

1 the main documents, correct?

2 A. I don't recall the words, but I did rely on it, yes.

3 Q. Okay. And you understand that the defendants have  
4 narrowed what are called their "obviousness combinations,"  
5 they've told you that?

6 A. I can't say as I recall.

7 Q. Okay. As of the priority date of the claimed  
8 inventions, Vachharajani was the source of all of the  
9 original data describing the role of cytochrome P450 enzymes  
10 in the metabolism of tasimelteon, correct?

11 A. As far as I know, based on what's in -- you know,  
12 publically available documents.

13 Q. That's right.

14 MR. STONE: Now, Mr. Weir, why don't you jump  
15 within this document to Page 10 of it, JTX-91 at 10.

16 BY MR. STONE:

17 Q. And let's look at what Vachharajani is saying.

18 MR. STONE: And can you pull up this paragraph  
19 here.

20 BY MR. STONE:

21 Q. It says: In studies with microsomes, overexpressing  
22 specific human CYP isoforms, BMS-214778.

23 That's what we now know as tasimelteon, correct?

24 A. Yes.

25 Q. Was primarily metabolized by CYP1A2, 1A2, 2D6 and

CROSS-EXAMINATION - DR. GREENBLATT

1 2C9.

2 Do you see that there?

3 A. I do.

4 Q. And jumping ahead a sentence, it says no metabolism  
5 of tasimelteon was observed following incubation with the  
6 same six enzymes we saw in Hardeland, the last of which is  
7 3A4, correct?

8 A. Correct.

9 Q. So while Hardeland says that the metabolism of  
10 tasimelteon was, quote, largely unaffected by those six  
11 enzymes, what a skilled artisan reading the primary source  
12 would see is that no metabolism was observed by BMS with  
13 those enzymes, correct?

14 That's what they would see there?

15 A. They would see it and see it's stated in different  
16 words.

17 Q. Well, let's have a conversation about the difference  
18 of words.

19 If my daughter comes home and tells me that  
20 she's primarily not using opiates or she comes home and  
21 tells me she's not using them, we're going to have two very  
22 different conversations.

23 Are you telling this Court primarily not  
24 metabolized by and not metabolized are synonyms?

25 A. I didn't say they were synonyms, but in this context

CROSS-EXAMINATION - DR. GREENBLATT

1       they are expressing the same thing.

2       Q.       And the primary source is the one we're looking at  
3       right now that says no metabolism was observed, correct?

4       A.       This is the primary source, yes.

5       Q.       Okay. Let's zoom out for a minute. Let's talk about  
6       how drugs are metabolized in the body, okay.

7                       Some drugs are metabolized in whole or in part  
8       in the liver, correct?

9       A.       Correct.

10      Q.       Of the drugs that are metabolized in the liver, many  
11      of them are metabolized by the CYP 450 family of enzymes  
12      that we have been talking about, correct?

13      A.       Correct.

14      Q.       Some drugs by some enzymes, some drugs by others,  
15      many drugs by more than one, correct?

16      A.       Correct.

17      Q.       Some drugs aren't really metabolized at all. You  
18      ingest them, they do whatever it is they do in your body,  
19      and you excrete them, correct?

20      A.       Correct.

21      Q.       Antibiotics are actually a pretty good example of  
22      that, correct?

23      A.       Some antibiotics, yes.

24      Q.       Right. And so many antibiotics come in, ideally kill  
25      the bacterium, and then get excreted out through the kidney



CROSS-EXAMINATION - DR. GREENBLATT

1 and the urine, correct?

2 A. Correct.

3 Q. Other drugs come through your body, do what they're  
4 going to do, go through the bile duct, and are excreted out  
5 in feces, correct?

6 A. Correct.

7 Q. And the divisions between out through the kidney, out  
8 through feces, or broken down in the liver are not quite  
9 that stark; some drugs are more than one of those, correct?

10 A. Correct.

11 Q. And for some drugs, for example, maybe 10 percent of  
12 the metabolism happens in the liver and the other 90 percent  
13 is just excreted out without having been metabolized,  
14 correct?

15 A. That's possible, yes.

16 Q. Okay. Let's talk next about what kind of tests  
17 scientists can do to study drug metabolism and drug  
18 interaction. Again, some vocabulary.

19 You're familiar with the terms in vitro and in  
20 vivo?

21 A. Yes.

22 Q. In vitro means in glass, correct?

23 A. In vitro means, to me, outside the body in some  
24 experimental system.

25 Q. We may be talking past each other, and that's my next

CROSS-EXAMINATION - DR. GREENBLATT

1 question.

2 But the Latin in vitro is "in glass," correct?

3 A. I don't know Latin so I don't have a comment on that.

4 Q. But you're beating me on German so far so we're  
5 keeping score.

6 In vivo means in a living organism, correct?

7 A. Yes.

8 Q. For an in vivo test, the organism doesn't need to be  
9 in a human. If you do the test in a rat, that's an in vivo  
10 test too, correct?

11 A. It's in vivo test in a rat.

12 Q. No dispute. I'm just trying to establish what's  
13 in-vitro and what's in vivo.

14 In a rat, that's in vivo.

15 A. Yes.

16 Q. Okay. One study that people can do to determine drug  
17 metabolism and possible risk of drug-drug interaction is  
18 what is called a mass balance study, correct?

19 A. It's possible to do a mass balance study, but that  
20 does not directly get at drug interaction.

21 Q. Right. What it gets at is pathway. What a mass  
22 balance study will tell us is how much of the drug is  
23 metabolized in the liver, how much is being excreted out in  
24 urine, how much is being excreted out in feces, correct?

25 A. And also what the specific metabolites are if there's

CROSS-EXAMINATION - DR. GREENBLATT

1 metabolism.

2 Q. Right. And let's just -- that word hasn't come up  
3 yet.

4 When a liver -- withdrawn?

5 Enzymes are things that act on substrates,  
6 correct?

7 A. Yes.

8 Q. One thing the enzyme might do is to overly  
9 anthropomorphize it, chop a piece off of the end, correct?

10 A. Yes, there can be cleavage, yes.

11 Q. Right. Enzymes catalyze the substrate; they do  
12 something to it, correct?

13 A. Yes, the enzymes are what caused the change in the  
14 substrate molecule, yes.

15 Q. Right. And the thing that is the result of that  
16 reaction is called a metabolite, correct?

17 A. Correct.

18 Q. It's the noun from metabolism. It's metabolite,  
19 correct?

20 A. Yes.

21 Q. Some enzymes metabolize some substrates and produce  
22 metabolites that have exactly the same beneficial properties  
23 as the drug itself, correct?

24 A. Yes, the same pharmacologic activity.

25 Q. Right. So merely knowing that an enzyme metabolizes

CROSS-EXAMINATION - DR. GREENBLATT

1 a substrate doesn't tell you whether that metabolite is, for  
2 practical purposes, different than the drug itself, correct?

3 A. Well, or whether it has the same -- it is different,  
4 but you don't know what its pharmacologic activity is.

5 Q. Right. And I am not looking to hide the ball.

6 Sometimes the metabolites are toxic, correct?

7 A. It's possible.

8 Q. Sometimes they're even better for your body than the  
9 drug itself, correct?

10 A. Well, they may have greater pharmacologic activity  
11 than the drug administered, yes.

12 Q. Right. In fact, there are drugs that are  
13 administered that are called prodrugs, where the drug itself  
14 is not active and the plan is that it will be metabolized  
15 and the metabolite will do the work, correct?

16 A. Correct.

17 MR. STONE: I don't know if we have the ability  
18 to do this, but trusting Mr. Weir, if we have plaintiff's  
19 demonstratives, can I get DDX-6.10?

20 And this is not a bad time for a break if it  
21 would help the Court.

22 THE COURT: Yeah, let's take a break then.

23 We're mid-morning.

24 MR. STONE: Thank you, Your Honor.

25 THE COURT: We'll come back in about 12 minutes.

CROSS-EXAMINATION - DR. GREENBLATT

1 I should warn you, you're on cross-examination  
2 so you shouldn't speak about the substance of the case with  
3 your counsel. All right?

4 THE WITNESS: Yes.

5 (Break taken.)

6 THE COURT: All right. You may proceed,  
7 Mr. Stone.

8 MR. STONE: Thank you, Your Honor.

9 I am told that before we broke, I referred to  
10 this as plaintiff's demonstrative 6.10. For the record,  
11 this is defendants' demonstrative 6.10.

12 THE COURT: Okay.

13 BY MR. STONE:

14 Q. Dr. Greenblatt, when we broke, we had just put this  
15 slide up, so let's start over with it.

16 You told us on your direct examination that FDA  
17 requires screening experiments to determine where the drug  
18 metabolism is likely to occur in the body, correct?

19 A. That's right.

20 Q. Could be the liver, could be the gut, could be  
21 elsewhere, correct?

22 A. It's possible, yes.

23 Q. What metabolites are likely to be formed and how  
24 quickly, correct?

25 A. Correct.

CROSS-EXAMINATION - DR. GREENBLATT

1 Q. And which CYP isoenzymes are likely involved in drug  
2 metabolism, correct?

3 A. Correct.

4 Q. And then you identified two different kinds of tests.  
5 One of them is an in-vitro experiment with liver microsomes,  
6 correct?

7 A. Correct.

8 Q. And the other is recombinant expression of particular  
9 isoenzymes, correct?

10 A. Yes.

11 Q. Vachharajani, the test from BMS that we've been  
12 looking at, is the second of those. It's the recombinant  
13 expression of particular isoenzymes, correct?

14 A. Correct.

15 Q. That kind of test can't tell you the relative  
16 contribution of each of those enzymes to tasimelteon  
17 metabolism in the body, correct?

18 A. It's an in-vitro test, and it gives you the relative  
19 contribution in that system.

20 Q. I'm sorry. Don't you need to do a liver microsome  
21 test to get relative contribution?

22 A. To complete the story, yes. You need to combine the  
23 two.

24 Q. Okay. And so in order to get relative contribution  
25 of the enzymes, vis-à-vis each other, even in vitro you need

CROSS-EXAMINATION - DR. GREENBLATT

1 to do both of these tests, correct?

2 A. You can get information from the recombinant  
3 expression of enzymes about the relative contribution out of  
4 context of a full liver.

5 Q. Hold on a second.

6 To get the true picture of how the various CYP  
7 enzymes contribute to tasimelteon metabolism using in-vitro  
8 tests, you have to do both of them, correct?

9 A. You get a different picture from one or the other  
10 versus combined.

11 Q. And you --

12 A. That's why you combine them.

13 Q. And you get a true picture from both.

14 A. I don't know what you mean by "true," but you get the  
15 information that's available.

16 Q. Okay. Okay.

17 Can you turn in the first document in the  
18 binder, which is your deposition, to Pages 52 and 53.

19 A. I'm sorry, is that the running page or the deposition  
20 page?

21 Q. That is a superb question and I have in mind the  
22 deposition page. So in the little boxes on each page,  
23 there's a page number in the corner.

24 A. Okay.

25 Q. Take a moment to read to yourself Pages 52 and 53.

CROSS-EXAMINATION - DR. GREENBLATT

1                   You'll agree with me, sir -- let me know when  
2                   you're ready.

3           A.       Yes, I'm ready.

4           Q.       On Page 53, we are talking about two different  
5                   studies and they're these: In-vitro experiments with liver  
6                   microsomes and recombinant expression with isoenzymes,  
7                   correct?

8           A.       Right.

9           Q.       Those are the two test being discussed, correct?

10          A.       Well, they are also tests with chemical inhibitors,  
11                   but these are the two general tests that's on the slide.

12          Q.       And are being discussed in your answer here.

13          A.       Yes.

14          Q.       Correct. I'm not suggesting they are the two tests  
15                   in the world; I'm suggesting they are the two you were  
16                   talking about at this passage in your deposition, correct?

17          A.       Yes.

18          Q.       Okay. And what you said at -- so looking at Page 53,  
19                   Line 5, the question was asked:

20                   "Q. So one methodology is to use recombinant  
21                   CYPs, correct?"

22          A.       Yes.

23          Q.       And you answered:

24                   "A. That's a piece of it. You need to combine  
25                   the methodologies to get -- to get the true picture."



CROSS-EXAMINATION - DR. GREENBLATT

1                   That was your answer, correct?

2           A.       That's right.

3           Q.       Right. And when I asked you today whether you need  
4           to combine the two to get the true picture you said, I don't  
5           know -- you don't know what I mean by "true picture,"  
6           correct?

7           A.       That's right. And I still don't.

8           Q.       Okay. But you know what you meant when you said it.

9           A.       That, I can't comment on, but...

10          Q.       Okay. Then let's move on.

11                   Let's switch to in vivo tests rather than in  
12          vitro.

13                   One of the things you can learn from an in vivo  
14          study, rather than an in vitro study, is the relative  
15          abundance of the relevant enzymes in the natural stage in a  
16          live human, correct?

17          A.       Are you talking about an in vivo study in which you  
18          would administer a drug to a human?

19          Q.       Well, why don't we start there.

20                   That's one of the things you could determine  
21          from that, correct?

22          A.       I'm sorry, I didn't -- I missed the question. Please  
23          try again.

24          Q.       Well, okay. I have to ask a favor, sir. We are on a  
25          clock. If I'm going to ask a question and you're going to

CROSS-EXAMINATION - DR. GREENBLATT

1 question back what I meant and then not remember what I  
2 asked, we're going to be here for a bit. So why don't we  
3 try to focus on the question.

4 Is that fair?

5 A. Sir, if I may, clock or no clock, I need to  
6 understand your question.

7 Q. Sure.

8 A. And when you ask one, I need to be able to  
9 understand it to answer it.

10 Q. Okay.

11 A. So I request that that be honored.

12 Q. Okay. I'm going to -- and I will honor that. I'm  
13 going to put a question to you now. Let's see how we do.

14 An in-vitro study in microsomes or recombinant  
15 enzymes can give you an estimate of the activity of a  
16 specific enzyme. But in order to determine what that means  
17 in an actual human context, you need to know exactly how  
18 much enzyme is present, correct?

19 A. That is correct. You need to know the abundance of  
20 the enzyme.

21 Q. Even where two drugs interact in a patient, the drugs  
22 can have a substantial interaction or a fairly mild one or  
23 somewhere in between, correct?

24 A. Correct.

25 Q. If you want to precisely delineate the quantitative

CROSS-EXAMINATION - DR. GREENBLATT

1 magnitude of the interaction between two drugs in a human  
2 being, you need to do an in vivo study, correct?

3 A. That is correct.

4 Q. And you need to know the magnitude of the interaction  
5 between two drugs in order to provide cogent advice as to  
6 what to do clinically, correct?

7 A. In some cases, yes.

8 Q. All right. Let's turn to your deposition at Page  
9 102, please. I'm going to ask you to read to yourself  
10 Page 101 and 102 --

11 MR. LUKAS: Just a second. Objection. Can you  
12 lay a foundation, Counsel?

13 MR. STONE: Of what?

14 MR. LUKAS: Are you impeaching him?

15 MR. STONE: Yes.

16 I mean, does the Court want me to ask him, did  
17 you give inconsistent testimony at your deposition?

18 THE COURT: Here's what I do.

19 MR. STONE: Sure.

20 THE COURT: Because I understand you all are  
21 very good lawyers, but here's what I do when it comes to  
22 inconsistent statement versus refresh your recollection.

23 MR. STONE: Which I'm not doing, I agree.

24 THE COURT: But I only know of what you're  
25 doing -- at least in my practice is for purposes of

CROSS-EXAMINATION - DR. GREENBLATT

1 refreshing recollection.

2 MR. STONE: Okay.

3 THE COURT: In my courtroom, and certainly as a  
4 trial lawyer, if a witness said something that was  
5 inconsistent with what the witness had said on a prior  
6 occasion, so if I asked the witness, well, you said the car  
7 was blue -- or I say to the witness, what color was the car,  
8 and the witness says, well, it was yellow, and I say, well,  
9 in fact, the car was blue, and he says, no, and then I'd  
10 say, well, you testified on a prior occasion that the car  
11 was blue, didn't you. And if the witness says no, then I  
12 confront the witness with the prior statement under oath,  
13 and that's how I would do it.

14 MR. STONE: I --

15 THE COURT: I don't think you have to go back  
16 through that, but in fairness to you because, frankly, the  
17 examination is very good, I'm only referring to that  
18 technically, perhaps other judges require different things,  
19 but in my courtroom I think you satisfied Rule 611 through  
20 614 by doing it that way, and so that's how I do it.

21 MR. STONE: And I --

22 THE COURT: And it's a -- if it's a question  
23 where the witness cannot recall, then what I would do is,  
24 and I think under the rules, you're required, you have to  
25 show the witness -- you can show the witness anything -- and

CROSS-EXAMINATION - DR. GREENBLATT

1 you can say, look at it yourself, then you take it back, and  
2 then you say, having seen that, does it refresh your  
3 recollection, and then you go from there.

4 That's how I would do it.

5 MR. STONE: I appreciate that, Your Honor, and,  
6 you know, ground rules in different ballparks.

7 THE COURT: That's right, exactly. That's  
8 why -- what I'm doing is since you asked me, and for the  
9 benefit of all lawyers, at least in my courtroom, that's how  
10 I would do it.

11 MR. STONE: And I will do it that way, Your  
12 Honor. I appreciate it.

13 Let me just look at the transcript for a moment,  
14 if I may.

15 THE COURT: While you're looking, typically what  
16 happens in these patents cases is, and I see it all the  
17 time, and you're not doing it, what lawyers do is they  
18 say -- they ask a question, they didn't get the exact answer  
19 they want, and they say, well, let's look at your  
20 deposition, and they put it on the screen and we have a  
21 debate about whether it's consistent and not inconsistent.

22 And that, I do not think, is the appropriate way  
23 to do it. You're not doing it that way.

24 So I don't have a problem with the way you're  
25 doing it, but that's the way I would do it.

CROSS-EXAMINATION - DR. GREENBLATT

1 MR. STONE: Thank you, Your Honor. A question:  
2 Can I be heard from here by the court reporter because I'm  
3 not at the mic.

4 THE REPORTER: Yes.

5 MR. STONE: Thank you.

6 BY MR. STONE:

7 Q. Dr. Greenblatt, I just asked you, just to reset the  
8 stage: And you need to know the magnitude of the  
9 interaction between two drugs in order to provide  
10 cogent advice as to what to do clinically, correct?

11 And your answer was: In some cases, yes.

12 Correct?

13 A. That's from today?

14 Q. That is from today.

15 A. Yes.

16 Q. And on a prior occasion, I asked the same question.  
17 The answer you gave didn't have the modifier about "in some  
18 cases," correct?

19 A. Is that in the transcript?

20 Q. Now I think we're somewhere between refreshing  
21 recollection and impeachment.

22 THE COURT: Go ahead.

23 BY MR. STONE:

24 Q. So, yes.

25 In Page 102 of your deposition at Line 12,

CROSS-EXAMINATION - DR. GREENBLATT

1     you're asked:

2                     "Q. Explain to me again why knowing the  
3                     magnitude is so important to this area of study."

4                     Do you see that there?

5     A.         Yes.

6     Q.         And the magnitude is the magnitude of interaction  
7                     between the enzymes, correct?

8     A.         Yes.

9     Q.         And your answer was:

10                    "A. In order to provide cogent advice as to  
11                    what to do clinically, you need to know how big the  
12                    interaction is. You also need to know whether it  
13                    makes any difference, but that's another story. But  
14                    you need to know how big the interaction is and what  
15                    the degree of variability between people exists and  
16                    the degree of interaction. And you need that  
17                    information to provide cogent clinical  
18                    recommendations."

19                    That was your testimony, correct?

20     A.         That was -- yes, that's correct.

21     Q.         Okay.

22                    And my colleague points out that I asked you  
23                    about the magnitude of the interaction between two enzymes.  
24                    We actually mean the magnitude of interaction between two  
25                    drugs, correct?

CROSS-EXAMINATION - DR. GREENBLATT

1 A. Yes.

2 Q. Thank you, sir.

3 Now, talking about the clinical options that you  
4 were referring to, the clinical options could be changing  
5 the dosage of one drug --

6 A. I'm sorry.

7 Q. Withdraw. I'll withdraw the question, sir.

8 We're starting a new question.

9 When considering drug-drug interactions, what to  
10 do about how two drugs interact with each other, the  
11 clinical options include change the dosage of one drug,  
12 change the dosage of both drugs, avoid one drug, avoid the  
13 other, special monitoring, perhaps, for adverse  
14 consequences; those are all clinical options, correct?

15 A. Those are among options, yes.

16 Q. Right. And you would want to know the magnitude of a  
17 drug-drug interaction to know whether any adjustment to a  
18 treatment regimen is warranted, correct?

19 A. It depends on the circumstances.

20 Q. I'm sorry, I didn't hear you.

21 A. It depends on the circumstances.

22 Q. Okay. You need to know whether the drug-drug  
23 interaction actually changes clinical outcomes for the  
24 patient before you can provide cogent advice as to what to  
25 do clinically, correct?



CROSS-EXAMINATION - DR. GREENBLATT

1 A. Yes, or at least what would be expected in terms of a  
2 clinical change.

3 Q. As of the priority date of these patents, there were  
4 no in vivo studies of tasimelteon metabolism, correct?

5 A. There were clinical studies, but the outcomes were  
6 not available in the public domain.

7 Q. Okay. I'll ask it that way.

8 As of the priority date, a skilled artisan would  
9 have no data at her fingertips about the in vivo aspects of  
10 tasimelteon metabolism, correct?

11 A. I believe that's correct, yes.

12 Q. There had been no data available to our skilled  
13 artisan about the magnitude of interaction between, say,  
14 CYP1A2 and tasimelteon, correct?

15 A. Between inhibitors?

16 Q. Withdrawn. That's a fair question. Withdraw.

17 As of the priority date from reading Hardeland  
18 and following up with Vachharajani, a skilled artisan would  
19 know that Vachharajani had found that CYP1A2 is one of four  
20 enzymes that metabolized tasimelteon in an in vitro assay,  
21 correct?

22 A. That's only part of it. But yes, they would have  
23 known that plus other things disclosed by Vachharajani.

24 Q. Okay. And the other things that are disclosed that  
25 you are referring to are all in the four corners of

CROSS-EXAMINATION - DR. GREENBLATT

1 Vachharajani, correct?

2 A. Four corners.

3 Q. Yeah, within the document.

4 A. Yes.

5 Q. Okay. And there were no in vivo data available about  
6 tasimelteon's interaction with a CYP1A2 inhibitor as of that  
7 date, correct?

8 A. Correct.

9 Q. There were no in vivo data about tasimelteon's  
10 interaction with a CYP1A2 inducer either, correct?

11 A. Or you mean CYP3A4?

12 Q. I don't. I actually meant the CYP1A2 inducer.

13 A. That's correct.

14 Q. Right. In fact, there were no data available for in  
15 vivo analysis of how tasimelteon interacted with any drug  
16 that upregulated or downregulated any enzyme as of the  
17 priority date, correct?

18 A. Correct. No direct in vivo data.

19 Q. Now, when you talked to us on direct, you told us  
20 that FDA says to start with in-vitro testing.

21 Did I hear you say that correctly, start?

22 A. Yes. My understanding is that that testing is  
23 required, you know, in the early preclinical days of --  
24 phases of drug development.

25 Q. I think you told us that doing those tests is, quote,

CROSS-EXAMINATION - DR. GREENBLATT

1 standard practice, correct?

2 A. Right.

3 Q. All right. If you turn in your binder to JTX-130,  
4 which should be the next document, this is a document  
5 entitled Guidance For Industry: Drug Interaction Studies,  
6 Study Design, Data Analysis, Implications For Dosing and  
7 Labeling Recommendations.

8 Do you see that there?

9 A. I do, yes.

10 Q. And then importantly it says: Draft guidance.

11 Do you see that there?

12 A. Yes. And on the top of each page it says: Not for  
13 implementation.

14 Q. Right. Now, you also know that FDA never actually  
15 finalizes the guidelines, they are also draft?

16 A. That's the general case, yes.

17 Q. Right. So, you know, there are some parts of the  
18 world in which it might matter that a document is called  
19 draft. We can agree here that it doesn't actually matter  
20 that it's called draft, people follow it any way because it  
21 never gets finalized.

22 A. Well, I do think it does make a difference, but  
23 whatever.

24 Q. Okay. That's fair.

25 MR. STONE: Let's turn to Page 20 of this

CROSS-EXAMINATION - DR. GREENBLATT

1 exhibit, Mr. Weir.

2 BY MR. STONE:

3 Q. And this is the FDA guidance -- or this is part of  
4 the FDA guidance you were talking about on your direct, this  
5 document, correct?

6 A. Yes.

7 Q. Okay. And so what we have up here --

8 MR. STONE: Can we zoom in at the top on  
9 Figure 2 and just the two lines below it.

10 THE WITNESS: Figure 2?

11 MR. STONE: Perfect, thank you.

12 You should be looking at this, sir, are you? On  
13 Page 20 of the document? I'm sorry?

14 Your Honor, I'm afraid he may have a different  
15 document. May I approach the witness?

16 THE COURT: Sure.

17 MR. STONE: Thank you.

18 People on both tables are telling me that I  
19 haven't yet offered this document into evidence. So let me  
20 do that.

21 This is JTX-130 and I offer it.

22 MR. LUKAS: No objection, Your Honor.

23 THE COURT: All right. It's admitted.

24 (JTX-130 admitted into evidence.)

25 MR. STONE: Thank you.

CROSS-EXAMINATION - DR. GREENBLATT

1 BY MR. STONE:

2 Q. What we see here at the top, you'll agree with me,  
3 sir, that this is a flow chart or a decision tree?

4 A. Yes, it's the beginning -- it's -- yes, the first  
5 phases of it.

6 Q. I'm sorry. I didn't hear you.

7 A. The first phases of the flow chart.

8 Q. But the whole page is a flow chart, agreed?

9 A. Yes.

10 Q. Okay. It starts with: Conduct in-vitro metabolism  
11 and drug-drug interaction studies in human tissues.

12 And for Phase 1 enzymes, it identifies a number  
13 of the CYP enzymes, including both 1A2 and the entire 3A  
14 family.

15 Do you see that there?

16 A. Yes, I see what that says.

17 Q. Okay.

18 MR. STONE: And hold on, Mr. Weir. Can you  
19 leave that up for a moment, Mr. Weir. And also bring up  
20 this below it.

21 BY MR. STONE:

22 Q. The flow chart ends with dosage adjustment needed,  
23 yes, no, correct?

24 A. Yes.

25 Q. All right. Let's leave it right there.

CROSS-EXAMINATION - DR. GREENBLATT

1 As of the priority date, one of the two kinds of  
2 in vitro assays we've been talking about had been conducted  
3 with respect to tasimelteon, correct?

4 A. Yes.

5 Q. The next question that the flow chart asks is:  
6 Investigational drug.

7 For us, that's tasimelteon, right? The  
8 investigational drug is tasimelteon?

9 A. Yes.

10 Q. I'm sorry. I didn't hear you.

11 A. Yes.

12 Q. Okay.

13 Is investigational drug a substrate of an enzyme  
14 responsible for greater than or equal to 25 percent of its  
15 systemic clearance.

16 Do you see that there?

17 A. Yes.

18 Q. Starting at the back, systematic clearance is how it  
19 exits the body, correct?

20 A. Yes.

21 Q. At this point in time, as of the priority date, we  
22 don't know the answer. There is no public data on whether  
23 tasimelteon is a substrate of an enzyme that is responsible  
24 for greater than 25 percent of tasimelteon systematic  
25 clearance, correct?

CROSS-EXAMINATION - DR. GREENBLATT

1 A. That's correct.

2 Q. As of the moment of the priority date, the skilled  
3 artisan has no way to get to even the third level of this  
4 decision tree, much less all the way to the bottom to decide  
5 whether a dosage adjustment is needed, correct? The data  
6 just aren't known?

7 A. There is data known, but the components of the tree  
8 are not complete at that point.

9 Q. Okay. And just to get an answer to my question, we  
10 don't yet have the ability as of the priority date to answer  
11 the question under this decision tree is a dosage adjustment  
12 needed, correct?

13 A. That's correct.

14 Q. Okay. Now, you have written on the ability to go  
15 from in-vivo data to predict in vivo results, correct?

16 A. To predict quantitative in-vivo results.

17 Q. Totally fair.

18 People have been trying in your field since at  
19 least the early 1970s to figure out how to take in-vitro  
20 data and predict the quantitative results that one would get  
21 in vivo, correct?

22 A. Correct.

23 Q. And you have published on that before, correct?

24 A. Correct.

25 Q. And, in fact, it is your opinion that we're not there

CROSS-EXAMINATION - DR. GREENBLATT

1 yet, correct?

2 A. That is the summary, yes.

3 Q. It's not only the summary, sir, it's the headline.

4 Let's look at PTX-683 in your binder. It's the next  
5 document.

6 Is this an article --

7 MR. STONE: Take it down, Mr. Weir. I have to  
8 put in evidence.

9 BY MR. STONE:

10 Q. Is this a document, sir, that you wrote?

11 A. Yes, and it says we're not there yet.

12 Q. Right.

13 MR. STONE: Now I offer PTX-683, Your Honor.

14 MR. LUKAS: No objection.

15 THE COURT: All right.

16 (PTX-683 admitted into evidence.)

17 MR. STONE: Just for the benefit of everyone,  
18 would you --

19 THE COURT: And it's admitted.

20 MR. STONE: I apologize, Your Honor.

21 BY MR. STONE:

22 Q. The title of the essay that you wrote is: In-vitro  
23 prediction of clinical drug interactions with CYP3A4  
24 substrates: We are not there yet.

25 Correct?



CROSS-EXAMINATION - DR. GREENBLATT

1 A. Correct.

2 Q. I want to talk to you for a moment about what your  
3 conclusion is with respect to the CYP1A2 patent. Okay.

4 A. Yes.

5 Q. A person having ordinary skill as of the priority  
6 date of the CYP1A2 patent would know from Hardeland and  
7 Vachharajani that in an in-vitro assay tasimelteon is  
8 metabolized by CYP1A2, correct?

9 A. Correct.

10 Q. There are lots of drugs that are metabolized in an  
11 in-vitro assay by CYP1A2 where you don't need to avoid  
12 concomitant administration with a CYP1A2 inhibitor, correct?

13 A. See, that I don't know. I don't know how the package  
14 inserts run with respect to 1A2 substrates being concomitant  
15 with fluvoxamine. I believe some of them have very strong  
16 warnings against it.

17 Q. Okay. And just to be clear, that's fine. Some of  
18 them absolutely do have a warning against concomitant  
19 administration, correct?

20 A. Yes.

21 Q. And every drug that is metabolized by CYP1A2 in whole  
22 or in part, that FDA has warned don't administer it with a  
23 CYP1A2 inhibitor, that warning is given on the basis of at  
24 least in vivo data, correct?

25 A. Not necessarily. There may be some advanced data

CROSS-EXAMINATION - DR. GREENBLATT

1 from in-vitro that would lead them to make the same  
2 recommendation.

3 Q. And whatever that advanced data is, if it exists, it  
4 was not in the art for tasimelteon, correct?

5 A. Some of it was.

6 Q. All right. Your opinion in this case, just to get it  
7 right, is that as of the moment of the priority date --

8 A. Yes.

9 Q. -- a skilled artisan would know from the fact that  
10 tasimelteon is metabolized by CYP1A2 in an in-vitro assay  
11 that there is a risk that there might be an interaction with  
12 a CYP1A2 inhibitor and they would simply avoid -- they would  
13 use caution, I think was your testimony, when  
14 coadministering them, correct?

15 A. They would use caution and they would avoid  
16 coadministration, yes, absolutely.

17 Q. Now, it might well turn out that the rest of the  
18 data, the in vivo data, would show that no such caution is  
19 needed and that coadministration was fine, correct?

20 A. That is a possibility, yes.

21 Q. Right. So what you're saying is the skilled artisan  
22 standing at the first step of that flow chart with respect  
23 to CYP1A2 should simply on the side of caution and decide  
24 don't coadminister? That is your opinion?

25 A. That in the universe of all other data, they would

CROSS-EXAMINATION - DR. GREENBLATT

1 most certainly take that approach.

2 Q. Right. And it might turn out that that approach is  
3 needlessly cautious, and unnecessary?

4 A. That is always a possibility, but remote in my view.

5 Q. Let's talk about CYP3A4 for a moment, okay?

6 A. Yes.

7 Q. A person reading -- strike that. Stay with me for a  
8 moment, sir.

9 The hypothetically skilled ordinary artisan in  
10 your hypothetical with respect to the CYP1A2 patent is going  
11 to start with Hardeland, correct?

12 A. That is the anchor for the purpose of these  
13 proceedings, but they're acting in a universe of all  
14 knowledge that's available on the topic.

15 Q. I understand that. The -- that same person is going  
16 to also look at Hardeland in connection with the 3A4 patent,  
17 correct?

18 A. And with the same qualification, in the constellation  
19 with everything else.

20 Q. I understand that.

21 And when they look at Hardeland, they will see a  
22 warning to not coadminister with a strong CYP1A2 inhibitor,  
23 correct?

24 A. I forget the wording. That's correct, yes, okay.

25 Q. I'll remind you.

CROSS-EXAMINATION - DR. GREENBLATT

1 A. Yes, I accept that.

2 Q. Well, no. Let's get the wording right. I shouldn't  
3 be describing the article. I should be telling you what it  
4 says.

5 What it says is: As -- withdrawn.

6 Reading from DTX-16.6.

7 As tasimelteon is metabolized by the CYP  
8 isoenzymes CYP1A2, 1A1, 2D6 and 2C9, coadministration of any  
9 drug that inhibits one of these isoenzymes should be  
10 regarded with caution, correct?

11 A. Okay. Yes, if that's what it says, then yes.

12 Q. And it doesn't say to regard with caution medications  
13 that either inhibit or induce 3A4? Not included in that  
14 paragraph, correct?

15 A. Correct.

16 Q. And what Vachharajani, the underlying article, says,  
17 is that tasimelteon isn't even metabolized by 3A4, correct?

18 A. Essentially correct, yes.

19 Q. Right.

20 So it is your view that the person of ordinary  
21 skill reading Hardeland and Vachharajani and seeing no  
22 evidence of CYP3A4 metabolism in-vitro, no caution against  
23 administering CYP3A4 is somehow going to seize on the  
24 sentence that it is structurally similar to ramelteon and go  
25 immerse themselves in Pandi-Perumal, which is about

CROSS-EXAMINATION - DR. GREENBLATT

1 ramelteon metabolism.

2 That's your opinion, right?

3 A. No, that's false.

4 Q. Okay. What is it that takes the skilled artisan in  
5 your view from a study about tasimelteon, which says it's  
6 not metabolized by 3A4 to the ramelteon literature?

7 A. I'm saying that the ordinary -- person of ordinary  
8 skill in the art would look at the totality of information  
9 available about tasimelteon and come to the conclusion that  
10 it was very probable that coadministration with rifampin  
11 would cause induction of tasimelteon metabolism and lowering  
12 of plasma levels to a possibly ineffective level.

13 Why do I say that?

14 Q. Yes.

15 A. Because I look at -- an ordinary skill in the art  
16 person looks at the constellation of available information.  
17 They look at ramelteon and what was the outcome of  
18 ramelteon's interaction with tasimelteon. The similarity,  
19 the close similarity of tasimelteon and ramelteon in  
20 structure, in site of action, in mechanism of action.

21 And put that all together and come to the  
22 conclusion that you better watch out that the metabolism of  
23 tasimelteon by CYP3A4, Vachharajani notwithstanding, is not  
24 excluded because of the nature of studies done with  
25 recombinant enzymes.

CROSS-EXAMINATION - DR. GREENBLATT

1 Q. And so what you mean by Vachharajani notwithstanding  
2 is, despite the fact that Vachharajani, the study of BMS of  
3 their own molecule, says that tasimelteon isn't metabolized  
4 by 3A4, the skilled artisan would look at everything that is  
5 known including all the ramelteon literature and all the  
6 things you just said, correct? That's what you mean by  
7 "notwithstanding"?

8 A. By "notwithstanding" I mean that despite what  
9 Vachharajani says and finds, they would still and -- they  
10 would expect and be concerned about an interaction of  
11 tasimelteon with rifampin and strong CYP3A4 inducers.

12 Q. Now, one of the things you told us on your direct  
13 examination is that you have actually spent a significant  
14 amount of your life professionally working with the  
15 development of ramelteon, correct?

16 A. No, I never said that.

17 Q. Then I misheard you and I apologize.

18 What was it you told us about your experience  
19 with ramelteon?

20 A. The question was: What drugs have you been involved  
21 in in the development process? And ramelteon was one of  
22 them.

23 Q. Okay. I'm sure that there's a distinction between  
24 what I asked and what you just said and I apologize. That's  
25 what I was trying to elicit, so let's try again.

CROSS-EXAMINATION - DR. GREENBLATT

1 What was your role in ramelteon development?

2 A. Yes. Yes, I believe before ramelteon was approved,  
3 the sponsor had done a study on the pharmacokinetics and  
4 clinical effects of ramelteon in healthy volunteers in  
5 relation to age and gender. So they had both  
6 pharmacokinetic and they had data of drug effects on humans.

7 And they wanted to get this data in shape, I  
8 don't know for the NDA submission, or for a publication.  
9 Certainly for a publication. So we worked with them on the  
10 data. We analyzed it ourselves, we talked, we took the raw  
11 data and we constructed a manuscript which was later  
12 published in the biomedical literature on this topic,  
13 coauthored by myself, others in my group and also at least  
14 one investigator from the sponsor.

15 Q. And just to situate it in time, that all happened  
16 before the priority date of this patent, correct?

17 A. Yes, that's correct.

18 Q. Okay. And so let's look in Hardeland at --

19 MR. STONE: Mr. Weir, please bring up DTX-16.3.

20 Thank you.

21 BY MR. STONE:

22 Q. Dr. Greenblatt, down here on the left at the bottom  
23 of 16.2, there's a section called "Synthesis and SAR."

24 Do you see that?

25 A. Yes.

CROSS-EXAMINATION - DR. GREENBLATT

1 Q. What's SAR?

2 A. Structure activity relationship. That's how I  
3 understand the abbreviation.

4 Q. Okay. Me too, but I thought I would ask.

5 And what we're looking at here, what follows is  
6 then a whole bunch of paragraphs about the structure of  
7 tasimelteon, correct?

8 A. Yes, and other things as well, yes.

9 MR. STONE: And if we pull up the bottom right  
10 corner of page 16.3.

11 BY MR. STONE:

12 Q. Now it's talking about the in-vitro binding affinity  
13 of tasimelteon for the MT-1 and MT-2 receptors.

14 You see that at the top of that?

15 A. Yes.

16 Q. And you know those to be receptors to which melatonin  
17 also binds in the suprachiasmatic nucleus?

18 A. In the active site in the brain, yes.

19 Q. All right.

20 It then says that the binding affinities for  
21 MT-1 and MT-2 receptors have been identified for several  
22 other melatonergic compounds, including 2 iodomelatonin,  
23 melatonin and ramelteon.

24 Do you see that?

25 A. Yes.



CROSS-EXAMINATION - DR. GREENBLATT

1 Q. And it says: Therefore, ramelteon demonstrates  
2 higher affinity for the MT-1 and MT-2 receptors compared  
3 with tasimelteon, correct?

4 A. Let me just see the numbers here.

5 Q. I'm not asking you whether it's right. I'm just  
6 asking --

7 A. Yeah, that's what it says.

8 Q. Right. Okay. And then it says: Ramelteon exhibits  
9 structural similarity to tasimelteon as these compounds  
10 share the dihydrobenzofuran, correct?

11 A. That's what it says, yes.

12 Q. That's that reference in Hardeland, to the fact that  
13 tasimelteon and ramelteon are structurally similar, correct?

14 A. That statement that you just said is correct.

15 Q. But when you -- that is the reference in Hardeland to  
16 the structural similarity between the two molecules,  
17 correct?

18 A. Yes.

19 Q. Right. It's not in any part of Hardeland that's  
20 talking about tasimelteon metabolism or drug-drug  
21 interactions, correct? That's not what that part of the  
22 study is?

23 A. I don't understand what you mean.

24 Q. Okay. Let's try it this way.

25 Hardeland has a bunch of different sections,

CROSS-EXAMINATION - DR. GREENBLATT

1 correct?

2 A. Yes.

3 Q. One is about metabolism, correct?

4 A. Yes.

5 Q. One's about structure, correct?

6 A. Yes.

7 Q. In the structure section, there's a sentence that  
8 says ramelteon is structurally similar to tasimelteon,  
9 correct?

10 A. Yes.

11 Q. Right. Ramelteon is not discussed in the metabolism  
12 section of Hardeland, correct?

13 A. I believe that's correct, but I --

14 Q. And there's certainly nothing in Hardeland that tells  
15 the skilled artisan go look at the ramelteon literature for  
16 drug-drug interactions, correct?

17 A. Not to my knowledge.

18 Q. Now, you told us that -- and you put up a slide that  
19 says -- well, withdrawn. You didn't.

20 You told us that ramelteon and tasimelteon have  
21 the same mechanism of action. I think I heard you say that  
22 both on your direct and just now, correct?

23 A. Correct.

24 Q. You're not offering an opinion in this courtroom as  
25 to how ramelteon treats the diseases for which it's approved

CROSS-EXAMINATION - DR. GREENBLATT

1 or tasimelteon treats Non-24, are you?

2 A. My testimony is that whatever actions they have on  
3 sleep, it is via the same receptors, interaction with the  
4 same receptors.

5 Q. Okay. And I want to be clear about that.

6 They both bind to MT-1 and MT-2, correct?

7 A. Correct.

8 Q. What they do through that binding and how they work  
9 is way beyond your area of testimony, correct?

10 A. Specifically, yes. But when they bind to the same  
11 receptor with high affinity, we are assuming that they have  
12 the same mechanism of action, whatever that action is.

13 Q. Okay.

14 A. That's obligatory. It has to be.

15 Q. Your testimony is that any two drugs that bind, those  
16 receptors have the same mechanism?

17 A. Not any two. I'm talking about tasimelteon and  
18 ramelteon.

19 Q. All right.

20 MR. STONE: And, Your Honor, this is nowhere in  
21 any of his expert reports.

22 THE COURT: But you asked him?

23 MR. STONE: That's fair.

24 THE COURT: You got what you asked.

25 MR. STONE: That's fair. I accept that.

CROSS-EXAMINATION - DR. GREENBLATT

1 BY MR. STONE:

2 Q. What is the bioavailability of ramelteon in its  
3 label? Do you know?

4 A. I don't know if it's in the label, but the number is  
5 about 3 percent, 3 to 4 percent.

6 Q. What's the bioavailability for tasimelteon?

7 A. It's in the range of what, 25 percent, I think. I'm  
8 not sure.

9 Q. Wouldn't you be surprised if it's more like 38?

10 A. Okay. It's 38.

11 Q. So what we know from that is that whatever is going  
12 on in the body, a lot more ramelteon is getting broken down  
13 than tasimelteon is?

14 A. It's saying that the absolute bioavailability is the  
15 fraction of an oral dose that reaches a systemic  
16 circulation.

17 Q. Right.

18 A. So those numbers are different and that's all it  
19 says.

20 Q. Okay. And, of course, a skilled artisan wouldn't  
21 have known either of those things?

22 A. They certainly would have known about ramelteon.

23 Q. Right.

24 But they wouldn't have known about tasimelteon  
25 because that wasn't available yet?

CROSS-EXAMINATION - DR. GREENBLATT

1 A. That's correct.

2 Q. Right.

3 Now, what did BMS conclude with the data from  
4 Vachharajani? Do you know?

5 A. What do you mean "conclude"?

6 Q. Okay. With respect to 3A4 metabolism, what was BMS's  
7 conclusion about the role of CYP3A4 metabolism in  
8 tasimelteon?

9 A. Are we going back to what Vachharajani says?

10 Q. I'm asking you first if you know what they concluded  
11 from Vachharajani.

12 A. By BMS --

13 THE COURT: I'm going to interrupt because this  
14 applies to both sides. You all seem at times to use  
15 Vachharajani as -- exactly the same as BMS.

16 Are you both sides comfortable with that?

17 MR. STONE: I didn't mean to do that, Your  
18 Honor, but --

19 THE COURT: And that's what I'm sensing you are  
20 doing now. Maybe you're not. But that's -- again, I think  
21 both of you all do that.

22 MR. STONE: Let me see if I can clear that, Your  
23 Honor. I apologize for leaving that donut hole. Let me see  
24 if I can fill it.

25 MR. LUKAS: And if I may interject, it may have

CROSS-EXAMINATION - DR. GREENBLATT

1 been just like be a courtesy for the court reporter, but I  
2 think it's undisputed that Vachharajani and the coauthors  
3 were from BMS.

4 THE COURT: And I get that, but it's like we  
5 have a 30(b)(6) rule. We have employees who don't always  
6 speak for the corporation. And I'm not a scientific person,  
7 but BMS might have a different view than one of its  
8 scientists and employees. I don't know. I don't really  
9 care as long as you're comfortable with it.

10 But if I'm the witness I don't know if he's  
11 thinking the same as I am.

12 MR. STONE: That's totally reasonable, Your  
13 Honor. Let me see if I can clear it up.

14 Mr. Weir, can you bring up JTX-91. And bring up  
15 the top section again.

16 BY MR. STONE:

17 Q. We're looking at Vachharajani, correct, sir?

18 A. Yes, sir.

19 Q. And the authors are identified as working at  
20 Bristol-Myers with an address for contacting them, correct?

21 A. Yes.

22 Q. From your experience in the industry, whenever people  
23 at a pharmaceutical company publish an article like this and  
24 identify themselves, that article has been cleared for  
25 review internally at the pharmaceutical company, correct?

CROSS-EXAMINATION - DR. GREENBLATT

1 A. Yes, that's my understanding.

2 Q. Let me now ask you to turn to PTX-613. This is a  
3 document that's already in evidence. It is what is called  
4 the investigator brochure for tasimelteon.

5 You were not here when Dr. Polymeropoulos  
6 testified, correct, sir?

7 A. Correct.

8 Q. Okay. Is this a document that they've ever shown you  
9 before?

10 A. I don't recall seeing it.

11 Q. Okay. Let me ask you to just turn quickly to page  
12 41.

13 MR. STONE: And Mr. Weir, would you bring up the  
14 top. I'm sorry, page 43 in the exhibit. I apologize. 43.

15 Can you bring up the top?

16 BY MR. STONE:

17 Q. It says from this internal BMS document: In-vitro  
18 metabolism investigated using genetically engineered cell  
19 lines expressing specific individual cytochrome P450 and  
20 isoenzymes indicating that what we now call tasimelteon was  
21 primarily metabolized by CYP1A2, 1A1, 2D6 and 2C9.

22 Do you see that there?

23 A. Yes.

24 Q. CYP 2A6, 2B6, 2C8, 2C19, and 2E1, and 3A4 did not  
25 metabolize tasimelteon.

CROSS-EXAMINATION - DR. GREENBLATT

1 Do you see that there?

2 A. Yes.

3 Q. And if you turn, Mr. Weir, in this exhibit to Page  
4 45.

5 And, actually, Mr. Weir, I apologize. I know  
6 what I'm about to do to you, put up -- let's go to the next  
7 page, page 46 of the exhibit.

8 And there's a section here entitled "In Vitro  
9 Metabolism Studies."

10 Do you see that, sir?

11 Dr. Greenblatt, I'm using the page numbers at  
12 the very bottom of each page where it says 46 of 90.

13 A. Oh, yes, okay.

14 Q. You see there's a section called "In Vitro Metabolism  
15 Studies"?

16 A. Yes.

17 Q. And the last word on the page is "the," right?

18 A. Yes.

19 Q. Let's go to the next page.

20 The metabolic profiles were also comparable  
21 between different in vitro techniques employed. What we now  
22 call tasimelteon was primarily metabolized by CYP1A, CYP1A2,  
23 CYP2D6, and CYP2C9. CYP2A6, 2B6, 2C8, 2C19, 2E1, and 3A4  
24 did not metabolize tasimelteon, correct?

25 Do you see that?



REDIRECT EXAMINATION - DR. GREENBLATT

1 A. Yes, that's what it says.

2 MR. STONE: Okay, I have no further questions.

3 Thank you.

4 THE COURT: All right. Redirect.

5 MR. LUKAS: Very brief, Your Honor.

6 REDIRECT EXAMINATION

7 BY MR. LUKAS:

8 Q. Dr. Greenblatt, you were asked just now some  
9 questions about Hardeland and Vachharajani and about their  
10 statements that tasimelteon was not metabolized by CYP3A4.

11 Do you recall that?

12 A. I do, yes.

13 Q. And in your opinion, would a person of ordinary skill  
14 in the art have felt that a drug-drug interaction between  
15 tasimelteon and rifampin was unlikely based on those two  
16 disclosures?

17 A. The interaction can't be excluded because induction  
18 causes a massive increase in the amount of enzymes, and you  
19 cannot exclude a major role of CYP3A4 in the induced state  
20 even if you can't detect it in the uninduced state.

21 Q. And is part of your analysis based on what was known  
22 about ramelteon?

23 A. Yes.

24 Q. And you obviously worked on ramelteon, but a question  
25 is: Would a person of ordinary skill in the art have been

REDIRECT EXAMINATION - DR. GREENBLATT

1 aware of what was known about the drug-drug interactions  
2 between ramelteon and rifampin and ramelteon and  
3 fluvoxamine?

4 A. Yes, absolutely.

5 Q. And why is that?

6 A. Because that's part of the prior art, and it's part  
7 of the central information that's needed to safely  
8 administer ramelteon. And it's in the product label and  
9 it's in the biomedical literature.

10 Q. Right. And were those drug-drug interactions between  
11 ramelteon and rifampin or ramelteon and fluvoxamine small or  
12 large?

13 A. They were large.

14 MR. LUKAS: I have no further questions, Your  
15 Honor.

16 THE COURT: Okay. It's a bench trial, so I get  
17 to ask some questions.

18 This in-vitro versus in vivo, sometimes things  
19 that show up in an in-vitro test, or concerns that are  
20 raised by an in-vitro test, may turn out to be not a concern  
21 when we have in vivo testing.

22 Is that fair?

23 THE WITNESS: That's fair, and the reverse as  
24 well.

25 THE COURT: Right. You also mentioned in-vitro

REDIRECT EXAMINATION - DR. GREENBLATT

1 precedes in vivo, usually; is that right?

2 THE WITNESS: Yes.

3 THE COURT: So why do we have in-vitro before we  
4 have in vivo testing?

5 THE WITNESS: Because it's inexpensive, you can  
6 get a lot of information in a short period of time at low  
7 cost, and you don't have to administer any drugs to humans.  
8 So you can get all of this advanced information that allows  
9 you to proceed safely with human testing.

10 THE COURT: Well, I want to pick up on that  
11 because -- so although it may be the case that you could  
12 have cautionary lessons that are inferred from in-vitro that  
13 turn out not to be of concern when you do in vivo, am I  
14 correct to assume that the results of in-vitro testing  
15 could, in fact, preclude in vivo testing?

16 In other words, you might have some result from  
17 an in-vitro test that raises such a safety concern that no  
18 one would approve or participate in clinical trial?

19 THE WITNESS: Yes, that is true, but it also  
20 depends on the kind of substrate drug you're talking about.  
21 If you're talking about a new drug that cures cancer --  
22 well, even if there is a big interaction that's evident from  
23 the in-vitro, you may proceed with caution and safeguards  
24 and all that if it is a breakthrough drug that's treating,  
25 you know, an important public health problem.

REDIRECT EXAMINATION - DR. GREENBLATT

1           On the other hand, if it's just a drug that's  
2           so-called "me too," well, then the sponsor might give up  
3           anyways. So it all depends on --

4           THE COURT: So, basically, and, you know, I  
5           don't have the scientific background you all do, it could be  
6           that I have an in-vitro test that shows a very high  
7           likelihood of, let's make it death, and yet you're saying  
8           the FDA would still approve in vivo and ultimately clinical  
9           testing of that?

10          THE WITNESS: Well, I think death is an extreme.

11          THE COURT: Okay.

12          THE WITNESS: The in-vitro might predict or show  
13          a -- that an interaction, a large interaction is likely.

14                 So for most drugs, the sponsor would say, you  
15                 know, why bother. There's just too much hassle. Or the FDA  
16                 may say, too much hassle.

17                 But if it's a breakthrough drug that's dealing  
18                 with a very important unmet need of public health, there may  
19                 be a way to proceed with proper caution and safeguards and  
20                 dose adjustments if it has an impact on public health.

21                 So it depends on the kind of drug you're dealing  
22                 with.

23          THE COURT: Okay. Thank you. You may step  
24          down.

25                 Oh, actually, have you ever testified before as

1 an expert?

2 THE WITNESS: Yes.

3 THE COURT: How many times?

4 THE WITNESS: It comes out to about once or  
5 twice a year over 55 years.

6 THE COURT: Okay. Thank you.

7 THE WITNESS: Thank you.

8 (Witness excused.)

9 MR. STONE: Your Honor, that concludes, I  
10 believe, the defendants' rebuttal case. They had called him  
11 out of order and whatever the response case, and we're now  
12 resuming our rebuttal case. We're have -- we're now in the  
13 third round.

14 That was their last witness. We are now  
15 resuming ours which we had begun and held open to let him  
16 testify.

17 THE COURT: Gotcha.

18 MR. STONE: And Vanda's next witness is  
19 Dr. Andrew Parkinson.

20 THE COURT: Okay.

21 MR. LUKAS: And Your Honor, we may call  
22 Dr. Emens to reply to Dr. Czeisler this afternoon.

23 THE COURT: All right.

24 MR. STONE: They had said they might. I didn't  
25 mean to preclude that.

1 May I get the binders?

2 THE COURT: Yes, please.

3 MR. STONE: Your Honor, I was under the  
4 impression that we were calling these witnesses and doing  
5 the Markman hearing today and that --

6 THE COURT: Well, the Markman hearing is not  
7 going to count against your time.

8 MR. STONE: No, no, I understand that. I meant  
9 in terms of --

10 THE COURT: But in terms of closing and  
11 evidence, right --

12 MR. STONE: Right.

13 THE COURT: -- you were -- I mean, we're -- and  
14 maybe there was a lot yesterday -- actually, hold on one  
15 second.

16 I should recalculate because I do believe that  
17 the argument yesterday, which apparently with this 12-hour  
18 32-minute estimate assumes that the time was split evenly  
19 among the parties, in terms of dealing with what I'll call  
20 the authentication issues associated with the  
21 clinicaltrials.gov, and I do think that time should all be  
22 against the defendants.

23 Because had we not -- I was basically giving an  
24 act of kindness allowing for measures to be made for the  
25 defendants to be able to appropriately authenticate those

1 documents, and I don't think that time should be allocated  
2 evenly.

3 Now, I have the defendants have 11 hours and  
4 4 minutes left, not counting a --

5 MR. STONE: Your Honor, excuse me. They've used  
6 11 hours, I presume, not have 11 hours left.

7 THE COURT: Oh, God. Yes, yes.

8 MR. STONE: Sorry, Your Honor.

9 THE COURT: Yeah. So we'll -- we're going to  
10 have to figure out a way to recalculate that.

11 So how much time do you have left right now in  
12 terms of evidence in your mind?

13 MR. STONE: Our calculation of what we have  
14 left, which is not what we're going to take, we will take  
15 less, but to answer the first question, we have us as having  
16 2 hours, 9 minutes and now 40 seconds left. But we will be  
17 done way less than that in terms of our case.

18 THE COURT: Well, we're counting closings.

19 And what about Mr. Rozendaal, what do you think  
20 you all have left?

21 MR. ROZENDAAL: I'm waiting to get the update  
22 right now, Your Honor. I want to be sure we're calculating  
23 it --

24 THE COURT: While you're doing that, you  
25 calculate it, this is -- is this your last one or this is

1 your second-to-last witness?

2 MR. STONE: Second-to-last witness, but this one  
3 is brief.

4 THE COURT: And very brief.

5 And then the direct on your next witness, what  
6 do you anticipate it being?

7 MR. GROOMBRIDGE: Well, Your Honor, it may be  
8 getting shorter right now, right. The last witness is Dr.  
9 Czeisler.

10 THE COURT: So short?

11 MR. GROOMBRIDGE: It would have been about 45 or  
12 50 minutes, but I may need to cut that down.

13 THE COURT: Okay. And you have just rebuttal  
14 and cross left?

15 MR. ROZENDAAL: We have just cross and rebuttal  
16 left, yes.

17 (Discussion held off the record between  
18 counsel.)

19 MR. ROZENDAAL: I'm told 3 hours and 30 minutes  
20 without yesterday's evidentiary fight, so I'm not sure  
21 exactly how much time the Court is tacking on to us for  
22 that.

23 MR. STONE: Right. And by the way, that is what  
24 we have them at as well, or within a couple of minutes.

25 THE COURT: All right. Let's hurry through this



1 witness and then we're going to recalculate.

2 But I don't have -- this case ought to be  
3 wrapped up evidentiary-wise in an hour and a half is what we  
4 have.

5 Mr. Rozendaal, you're not calling any other  
6 witnesses? There's potentially a small witness in rebuttal.

7 MR. ROZENDAAL: Correct. And we can do it. I'm  
8 not saying we need any more time than that --

9 THE COURT: Well, all I know is right now I have  
10 been handed a chart which says that the plaintiff has used  
11 12 hours and 32 minutes, that the defendant has used 11  
12 hours and 4 minutes. All right. For a total -- so a total  
13 of 23 hours and 36 minutes. All right.

14 What do you all -- what's your total?

15 MR. STONE: We have 2 hours and now 7 minutes  
16 left in your calculation, Your Honor.

17 MS. JACOBS: And, Your Honor, we really were  
18 unsure how the Court was calculating -- there, obviously,  
19 was a lot of time on evidentiary disputes.

20 THE COURT: And they are split in half as a  
21 general rule, right, so...

22 If your time doesn't include evidentiary  
23 disputes, well, then, that's what the problem is.

24 MS. JACOBS: I believe it did, Your Honor.

25 THE COURT: Okay. So I'm told the amount of

1 argument regarding the authenticity took 31 minutes, so that  
2 means that -- all right.

3 According to what we have is the plaintiff has  
4 used 12 hours and 1 minute, which would give them an hour  
5 left, and that the defendant has used 11 hours and  
6 34 minutes, which would give it an hour and a half,  
7 ballpark. That's what we have. All right.

8 Now it doesn't include closing -- I mean, it  
9 should include closing arguments. Let's just get to --  
10 it's -- let's get through it.

11 MR. STONE: Your Honor, may we take a two-minute  
12 break so we can ratchet back the testimony and get both  
13 witnesses done within an hour, which we'll do?

14 THE COURT: Yeah. I'm not going to hold you to,  
15 just -- I mean, yeah. I mean, I'll do that. I mean, look.  
16 If anybody is going to tell me, and I'll listen, that you're  
17 prejudiced by this, you can tell me, but I don't think you  
18 all are.

19 MR. STONE: Your Honor, I'm confident we could  
20 put it on with a little bit of leeway beyond that, but I  
21 don't want to ask for that. So if we take five minutes, we  
22 may be able to come in just under it. And if at that point  
23 we go over a couple of minutes, I'm hopeful the Court will  
24 be receptive to it, but I'd like to see if we can shorten  
25 it.

DIRECT EXAMINATION - DR. PARKINSON

1 THE COURT: Okay. Mr. Rozendaal?

2 MR. ROZENDAAL: That's fine, Your Honor.

3 THE COURT: And you're okay with the time?

4 You're going to be able to do it?

5 MR. ROZENDAAL: Yeah, we'll be able to get it  
6 done.

7 THE COURT: All right. Then we'll take a  
8 10-minute break. We'll come back at 11:40.

9 (Recess taken.)

10 THE COURT: All right. Have a seat.

11 ANDREW PARKINSON, having been called on the part  
12 and behalf of the Plaintiff as a witness, being first duly  
13 sworn under oath, testified as follows:

14 DIRECT EXAMINATION

15 BY MR. KLEIN:

16 Q. Dr. Parkinson, do you have a white binder in front of  
17 you?

18 A. Yes, I do.

19 Q. Dr. Parkinson, what do you do for a living?

20 A. I'm an adjunct professor at the University of Kansas  
21 Medical Center, and I'm the founder and CEO of XPD  
22 Consulting.

23 Q. What does XPD Consulting do?

24 A. It is a follow-on from a previous company I founded  
25 called XenoTech that offered services in drug metabolisms,

DIRECT EXAMINATION - DR. PARKINSON

1 drug-drug interactions, drug development. XPD is a  
2 follow-on in which we do that in a consulting capacity.

3 Q. Have you run drug-drug interaction studies before?

4 A. Yes, many, many, many times.

5 Q. And was that for or on behalf of pharmaceutical  
6 companies?

7 A. Yes.

8 Q. Have you also assisted pharmaceutical companies to  
9 interpret the results of drug-drug interaction studies?

10 A. Yes, that's one of the major activities of our  
11 company.

12 Q. Can you turn to PTX-827 in your binder, please.

13 A. Yes.

14 Q. What is it?

15 A. It's my curriculum vitae.

16 MR. KLEIN: Your Honor, I'd like to offer  
17 PTX-827 into evidence.

18 MR. COBLENTZ: No objection.

19 THE COURT: It's admitted.

20 (PTX-827 admitted into evidence.)

21 BY MR. KLEIN:

22 Q. Dr. Parkinson, under Employment, with the entry it  
23 starts in 1999, it says: Adjunct professor of pharmacology  
24 and toxicology at Kansas University Medical Center.

25 A. Correct.

DIRECT EXAMINATION - DR. PARKINSON

1 Q. Is that a role that you still hold?

2 A. I went from assistant to associate to full professor,  
3 and now I am an adjunct professor.

4 Q. You were here when Dr. Greenblatt was asked some  
5 questions about the paper that's referred to as the  
6 Vachharajani paper or the Vachharajani study, correct?

7 A. I was, yes.

8 Q. Are you familiar with the type of in-vitro  
9 recombinant CYP study that Vachharajani was talking about?

10 A. Yes, it was a very common study we conducted at  
11 XenoTech. It's a very common study. And I currently  
12 consult on it.

13 Q. Have you ever run a study like that yourself?

14 A. Hundreds of times.

15 Q. And have you -- was that done for pharmaceutical  
16 companies?

17 A. Yes.

18 Q. Was that done in the context of a drug development  
19 process for pharmaceutical companies?

20 A. It was, yes.

21 MR. KLEIN: Your Honor, I'd like to offer  
22 Dr. Parkinson as an expert in drug-drug interaction  
23 research, pharmacokinetics, and pharmacology.

24 MR. COBLENTZ: No objection.

25 THE COURT: All right.

DIRECT EXAMINATION - DR. PARKINSON

1 BY MR. KLEIN:

2 Q. And Mr. Weir, can you -- well, Dr. Parkinson, have  
3 you prepared a set of slides to assist you with your  
4 testimony today?

5 A. I did.

6 MR. KLEIN: Mr. Weir, can you pull up PTX-10.3.

7 BY MR. KLEIN:

8 Q. And Dr. Parkinson, what are the issues that you plan  
9 on testifying about today?

10 A. They are listed here. I'm going to talk about  
11 Claim 14 of the '829 patent. That's the one concerning the  
12 effects of CYP1A2 inhibitor's exposure to tasimelteon.

13 And the second one is Claim 4 of the '910  
14 patent. That deals with the effects of rifampin or  
15 rifampicin on exposure to tasimelteon.

16 Q. And Dr. Parkinson, do you agree with Dr. Greenblatt's  
17 opinion that a skilled artisan who happened to come upon the  
18 Hardeland reference would then turn to the Vachharajani  
19 study?

20 A. With respect, Your Honor, no, I disagree with that  
21 assessment.

22 MR. KLEIN: Mr. Weir, can you please pull up  
23 PTX-10.9.

24 BY MR. KLEIN:

25 Q. So Dr. Parkinson, in the top panel -- well, what are

DIRECT EXAMINATION - DR. PARKINSON

1     you showing us on this slide?

2     A.       These are two excerpts from the Hardeland paper. One  
3     is from the text of the report, that's the top portion. At  
4     the end of that is a citation, 867425, and in the list of  
5     citations you see this is referring to the Vachharajani  
6     study.

7     Q.       And do you think that a skilled artisan who is  
8     reading the Hardeland paper in regards to the CYP metabolism  
9     of tasimelteon would then look to the Vachharajani paper?

10    A.       I would think an artisan would go to the primary  
11    source, which is the Vachharajani study.

12            THE COURT: So we have the same testimony we  
13    just got from the last expert, right, on that?

14            I just wanted to say, because when we just  
15    talked about time, I think I got that point.

16            MR. KLEIN: Your Honor, the issue was that I  
17    think Dr. Parkinson misheard my earlier question. I did not  
18    plan on using this slide. I planned on proceeding without  
19    it, but --

20            THE COURT: Okay.

21            MR. KLEIN: So Mr. Weir, can you please turn to  
22    PDX-10.10.

23    BY MR. KLEIN:

24    Q.       Dr. Parkinson, is this a slide you prepared?

25    A.       Yes.

DIRECT EXAMINATION - DR. PARKINSON

1 Q. What kind of study did Vachharajani run?

2 A. He examined a panel of individual recombinant human  
3 cytochrome P450 enzymes for their ability to metabolize  
4 tasimelteon.

5 Q. Is that what you are showing us with the top panel?

6 A. That's the summary of the result.

7 Q. That's at JTX-91 at Page 12, correct?

8 A. Yes.

9 Q. And in the bottom panel, you've culled out the  
10 language from Vachharajani. The relative contributions of  
11 each CYP isoform could not be determined.

12 Well, before we get there, what kind of --  
13 what's a study like the one done in Vachharajani good for?  
14 What would it be used for?

15 A. It's a very good test-tube experiment to answer the  
16 question, can a specific cytochrome P450 enzyme metabolize  
17 an investigational drug, which would be tasimelteon in this  
18 case.

19 Q. Okay. And then the second panel now on your slide,  
20 what does it mean, "the relative contributions of each CYP  
21 isoform could not be determined"?

22 A. So in the first panel, you see Vachharajani  
23 identified four enzymes that can metabolize tasimelteon, but  
24 he discloses their relative contribution, which one was a  
25 minor contributor, which one was a major, could not be



DIRECT EXAMINATION - DR. PARKINSON

1 determined from this experiment.

2 Q. Why would a skilled artisan care about relative  
3 contribution of the individual CYP enzymes?

4 A. Well, because an enzyme that contributes only a  
5 negligible amount would not raise any clinical concerns  
6 compared with an enzyme that dominated the metabolism of a  
7 drug that would be more of a concern in terms of clinical  
8 benefits.

9 Q. And does the relative contribution of the enzyme,  
10 would that also inform how exposure to the study drug would  
11 be affected?

12 A. It's part of the puzzle. You need to know at least  
13 two things. One, what is the relative contribution of each  
14 active enzyme to the metabolic clearance by cytochrome P450;  
15 and then you need the greater context: What is the relative  
16 contribution of cytochrome P450 dependant elimination to all  
17 pathways of elimination.

18 Q. And did you prepare a slide explaining that system?

19 A. Yes, I did.

20 MR. KLEIN: Mr. Weir, could you please pull up  
21 PDX-10.12.

22 BY MR. KLEIN:

23 Q. And Dr. Parkinson, what are you showing us on this  
24 slide?

25 A. In the top part of this slide, I'm showing the three

DIRECT EXAMINATION - DR. PARKINSON

1 major pathways by which drugs are eliminated from the body,  
2 or cleared from the body.

3 Some drugs, unchanged, are passed through the  
4 kidney and are eliminated in urine. We call this renal  
5 clearance. Some drugs go into bile and are excreted in  
6 feces. This is biliary clearance. And some drugs are  
7 broken down by what we call drug-metabolizing enzymes. That  
8 represents metabolic enzymes.

9 Q. Where in this schematic does clearance by CYP enzymes  
10 occur?

11 A. That's in the bottom left-hand corner.

12 Q. Is that oxidation CYP?

13 A. Yes.

14 Q. And you've written on your slide: Single CYP greater  
15 than or equal to 25 percent of overall clearance, question  
16 mark.

17 A. Correct.

18 Q. What does that mean?

19 A. This is the industry standard for assessing whether  
20 there is to be concern over cytochrome P450 inhibitor or  
21 inducer having a meaningful effect on exposure to the drug.  
22 So we're asking the question, is there a single cytochrome  
23 P450 enzyme that contributes 25 percent or more -- and this  
24 is the key part -- to overall clearance.

25 So we're looking at all possible clearance

DIRECT EXAMINATION - DR. PARKINSON

1 pathways, is it responsible for 25 percent of overall  
2 clearance.

3 Q. And was it known in the prior art the relative  
4 contribution of these different clearance pathways for  
5 tasimelteon?

6 A. No, we knew neither their relative contribution to  
7 the small box nor their contribution to the overall picture.

8 Q. What kind of study would provide the type of data a  
9 skilled artisan would need to ascertain the relative  
10 contribution of these different clearance pathways?

11 A. That's called a mass balance study. So the drug is  
12 administered to human subjects, we look at the concentration  
13 of the drug and its metabolites in blood, in urine, and in  
14 feces, and those samples are collected until most,  
15 90 percent, hopefully, plus of the drug is eliminated from  
16 the body.

17 Q. And without that kind of information, how would a  
18 skilled artisan know if it was even possible for a CYP  
19 inhibition or induction to result in a drug-drug  
20 interaction?

21 A. You have no basis for knowing that.

22 MR. KLEIN: And Mr. Weir, can you please turn to  
23 PDX-10.14.

24 BY MR. KLEIN:

25 Q. And Dr. Parkinson, this slide says: Additional

DIRECT EXAMINATION - DR. PARKINSON

1 information needed to assess potential drug-drug  
2 interactions.

3 A. Correct.

4 Q. Have we already discussed the first two rows?

5 A. Yes.

6 Q. And so the last row says: Formation of metabolites.

7 Why would a skilled artisan care about the formation of  
8 metabolites in trying to assess a drug-drug interaction?

9 A. So, many drugs are converted to metabolites that  
10 share the same pharmacologic activity as the parent drug, so  
11 we may have a pharmacokinetic interaction. So a second drug  
12 might inhibit or reduce the metabolism in the drug, and what  
13 happens is we may see a change in exposure to the parent  
14 drug, but we see a reciprocal change in exposure to the  
15 metabolites. And because both are contributing to the  
16 therapeutic efficacy, there is no change in that therapeutic  
17 efficacy despite a pharmacokinetic interaction, despite a  
18 change in exposure to the parent drug.

19 So we want to know, are metabolites  
20 pharmacologically active.

21 Q. And so zooming out a little bit, is it possible for a  
22 study to show, an in-vitro study, to show that a drug is  
23 metabolized by a certain enzyme, or even a drug-drug  
24 interaction in-vitro, but then inside the human body you  
25 don't see a similar effect?

DIRECT EXAMINATION - DR. PARKINSON

1 A. Yes.

2 Q. And did you prepare -- well, before we get to that.

3 Can you turn to PTX-394 in your binder, please.

4 A. Yes.

5 Q. And what is this?

6 A. Have I have got the right one? This is a publication  
7 by Engel on in-vitro metabolism of antipyrine.

8 Q. And did you rely this paper in forming your opinions?

9 A. Yes.

10 MR. KLEIN: Your Honor, I offer PTX-394 into  
11 evidence.

12 MR. COBLENTZ: No objection.

13 THE COURT: Admitted.

14 (PTX-394 admitted into evidence.)

15 BY MR. KLEIN:

16 Q. And what is antipyrine in the title?

17 A. It's an antifever drug.

18 Q. And what is this paper about?

19 A. This paper describes in-vitro studies that examine  
20 which particular cytochrome P450 enzymes were involved in  
21 the metabolism of antipyrine. And we're using recombinant  
22 cytochrome P450 enzymes and human microsomes that establish  
23 that CYP3A4 was one of the prominent enzymes, in fact, the  
24 major enzyme in the metabolism of antipyrine.

25 Q. And can you turn to PTX-393 in your binder, please.

DIRECT EXAMINATION - DR. PARKINSON

1 A. Yes.

2 Q. And what is it?

3 A. This is a paper by Blyden that is coauthored by  
4 Dr. Greenblatt.

5 Q. And did you rely on this paper in forming your  
6 opinions in this case?

7 A. I did, yes.

8 MR. KLEIN: Your Honor, I offer PTX-393 into  
9 evidence.

10 MR. COBLENTZ: No objection.

11 THE COURT: Admitted.

12 (PTX-393 admitted into evidence.)

13 BY MR. KLEIN:

14 Q. What is this paper about, Dr. Parkinson?

15 A. So this is a clinical drug interaction study of  
16 antipyrine with the CYP3A4 inhibitor.

17 THE COURT: And spell antipyrine for the court  
18 reporter.

19 THE WITNESS: Yes. A-n-t-i-p-y-r-i-n-e.

20 MR. KLEIN: And, Mr. Weir, can you please pull  
21 up PDX 10.15.

22 BY MR. KLEIN:

23 Q. And Dr. Parkinson, what are you showing us on this  
24 slide?

25 A. So this is a summary of the two studies, so on the

DIRECT EXAMINATION - DR. PARKINSON

1 left we have the Engel study. That was conducted in-vitro.  
2 This is the test tube interaction. What Engel showed is  
3 that ketoconazole, the CYP3A4 inhibitor, inhibited the  
4 formation of the three metabolites from antipyrine by 85, 65  
5 and 87 percent.

6 Meaning CYP3A4 was contributing 85 percent,  
7 65 percent, 87 percent of metabolism to the formation of  
8 those metabolites. This is a very strong in-vitro  
9 interaction.

10 But on the right in the Clinic, Dr. Greenblatt's  
11 study confirmed a previous study that even at a high dose  
12 ketoconazole does not affect the clearance of antipyrine.

13 Q. Would a skilled artisan have been aware of this  
14 phenomenon?

15 A. Yes, it's very common.

16 Q. Are there any other examples you can provide for the  
17 Court of seeing one kind of interaction in-vitro, but a  
18 different kind of interaction or no interaction in the human  
19 body?

20 A. Yes.

21 THE COURT: Before you do, isn't ketoconazole  
22 like a cream or something for skin?

23 THE WITNESS: It's an antifungal.

24 THE COURT: And this is the same Dr. Greenblatt  
25 that just testified?

DIRECT EXAMINATION - DR. PARKINSON

1 THE WITNESS: Yes.

2 THE COURT: Okay.

3 BY MR. KLEIN:

4 Q. Dr. Parkinson, can you provide the Court with any  
5 real-world examples of seeing one kind of interaction in  
6 vitro but then seeing a different kind or no interaction  
7 within the human body?

8 A. Yeah. So we have, as you can appreciate, a very  
9 large number of over-the-counter drugs, drugs that could be  
10 obtained without a prescription. And the fact they are  
11 over-the-counter means they are safe under a variety of  
12 conditions.

13 So just to give you one example, if you buy  
14 Tylenol, the in-vitro study will tell you Tylenol is  
15 metabolized CYP1A2, CYP2E1 and CYP3A4, but there are no  
16 meaningful interactions of drugs with Tylenol. Which is why  
17 it's an over-the-counter.

18 Q. Thank you.

19 MR. KLEIN: Your Honor, I thought that I offered  
20 PTX-393 and 394 I failed to do so.

21 I offer PTX-393 and PTX-394 into evidence.

22 MR. COBLENTZ: No objection.

23 THE COURT: All right. They're admitted.

24 (PTX-393 admitted into evidence.)

25 (PTX-394 admitted into evidence.)



DIRECT EXAMINATION - DR. PARKINSON

1 BY MR. KLEIN:

2 Q. Dr. Parkinson, I'd like to shift gears to now the  
3 subject matter of Claim 4 of the '910 patent.

4 MR. KLEIN: Mr. Weir, could you please pull up  
5 PDX-10.18.

6 BY MR. KLEIN:

7 Q. And this is the claim from the '910 patent that you  
8 analyzed, correct?

9 A. Correct.

10 Q. And do you see in Claim 1 the language says: Thereby  
11 avoiding reduced exposure to tasimelteon caused by induction  
12 of CYP3A4 by rifampicin?

13 A. Yes, I see that.

14 Q. Would exposure by tasimelteon be affected by a 3A4  
15 inducer if tasimelteon was not metabolized by CYP3A4?

16 A. No, it would not.

17 MR. KLEIN: And Mr. Weir, could you please pull  
18 up PDX-10.19.

19 BY MR. KLEIN:

20 Q. Dr. Parkinson, how do you think a skilled artisan  
21 would interpret the statements from Vachharajani and  
22 Hardeland about whether CYP3A4 metabolizes tasimelteon?

23 A. Well, the Vachharajani study indicates that CYP3A4  
24 does not metabolize tasimelteon. And in Hardeland paper, he  
25 raises no concern about the effect of a CYP3A4 inducer or

DIRECT EXAMINATION - DR. PARKINSON

1 inhibitor on exposure to tasimelteon.

2 MR. KLEIN: And Mr. Weir, could you please pull  
3 up PDX 10.20.

4 BY MR. KLEIN:

5 Q. Would a skilled artisan have had any reason to doubt  
6 the findings of Vachharajani that tasimelteon is not  
7 metabolized by CYP3A4?

8 A. In my opinion no, for the reasons listed here. Can I  
9 go through them?

10 Q. Yes, please.

11 A. First of all, studies with recombinant enzymes have a  
12 good reputation of providing a reliable yes/no answer to the  
13 question can a particular enzyme metabolize an  
14 investigational drug.

15 In the Vachharajani study, this was a nicely  
16 controlled study, they verified that each and every  
17 individual cytochrome P450 enzyme was functional. They did  
18 this with known substrates or what we call "positive  
19 controls." They saw a typical result for this type of  
20 study. Some enzymes were active, some enzymes were  
21 inactive.

22 But also it's unlikely you would underestimate  
23 the contribution of CYP3A4 to metabolism of a drug. We run  
24 into a problem that is specific to CYP3A4. And that problem  
25 is we tend to overestimate its contribution because of its

CROSS-EXAMINATION - DR. PARKINSON

1 unique characteristics.

2 CYP3A4 has what we call high affinity, low  
3 capacity. Which means as you keep increasing the drug  
4 concentration of the test tube, it keeps metabolizing the  
5 drug faster and faster.

6 With most other cytochrome P450 enzymes, they  
7 reach a plateau and so they cannot keep contributing to the  
8 metabolism of a drug of high concentrations. And this is  
9 relevant to the tasimelteon or Vachharajani study because  
10 they did, in fact, use a high concentration of tasimelteon  
11 in the in-vitro state.

12 Q. Thank you.

13 MR. KLEIN: All right. Your Honor, I have no  
14 further questions.

15 THE COURT: All right. Cross.

16 CROSS-EXAMINATION

17 MR. COBLENTZ: May I proceed, Your Honor?

18 THE COURT: Yes.

19 BY MR. COBLENTZ:

20 Q. Good afternoon, Dr. Parkinson.

21 A. Good afternoon.

22 Q. How are you?

23 Dr. Parkinson, you've never prescribed medicine;  
24 is that correct?

25 A. No, I'm not an M.D.

CROSS-EXAMINATION - DR. PARKINSON

1 Q. You don't have the ability to prescribe medicine; is  
2 that correct?

3 A. I don't have the qualifications, correct.

4 Q. Now, as a part of your analysis and Dr. Greenblatt's  
5 analysis you've heard the term "reasonable expectation of  
6 success"; is that correct?

7 A. Yes.

8 Q. And it's your position that you would need to meet  
9 FDA requirements for determining a drug-drug interaction in  
10 order to have a reasonable expectation of success of a  
11 drug-drug interaction; is that correct?

12 A. Okay. First of all, the FDA doesn't have  
13 requirements. The FDA makes nonbinding recommendations  
14 that's at the top of every page of every guidance. So these  
15 are not requirements.

16 The FDA guidance reflects the industry standard  
17 that the trigger to consider doing an in vivo clinical drug  
18 interaction study related to the cytochrome P450 is when an  
19 individual cytochrome P450 enzyme contributes 25 percent or  
20 more to the overall clearance of the drug to the body.

21 Q. Right. So in your deposition that we had, I'm going  
22 to try to refresh your recollection here, I asked you a  
23 question about whether it was your position that you would  
24 need to meet FDA requirements for determining a drug-drug  
25 interaction in order to have a reasonable expectation of

CROSS-EXAMINATION - DR. PARKINSON

1 success of a drug-drug interaction.

2 Do you remember that?

3 A. No, I don't.

4 Q. Okay. Let's turn to your deposition, which should be  
5 in the front of your binder.

6 A. Very good.

7 Q. And if we go to the Parkinson deposition, we go to  
8 page 135 and we look at lines 14 through 19.

9 Let me know when you're there.

10 Okay. And here it says:

11 "Question: And so I'm asking you again because  
12 you come back to the FDA requirement, do you need to meet  
13 FDA requirements in order to have a reasonable expectation  
14 of success of a drug-drug interaction?"

15 And your answer was: "Well, I would say yes."

16 Do you see that?

17 A. I do. That was probably the fifth answer I'd given  
18 to the same question you asked, so if you read the previous  
19 two pages, you just kept asking and I slipped up and  
20 admitted that point, which I take back.

21 Q. And is it your position that you need to conduct a  
22 clinical study demonstrating a drug-drug interaction in  
23 order to have a reasonable expectation that a drug-drug  
24 interaction takes place? Is that correct?

25 A. Yes. Not only do I believe that, the FDA believes

CROSS-EXAMINATION - DR. PARKINSON

1       that, too.

2       Q.       Now, a clinical study, that would give a person of  
3       ordinary skill in the art, it would give them more than a  
4       reasonable expectation of success, it would absolutely  
5       determine if there was a drug-drug interaction; is that  
6       correct?

7       A.       It would be the definitive information on the  
8       drug-drug interaction, yes.

9       Q.       And so it would absolutely determine if there was a  
10      drug-drug interaction, correct?

11      A.       Yes.

12      Q.       Now, when a pharmaceutical company is looking at  
13      drug-drug interactions for an investigational new drug, you  
14      would you agree with me that they typically start with  
15      in-vitro studies to investigate those drug-drug  
16      interactions; is that correct?

17      A.       Yes, that's very common practice.

18      Q.       And a POSA would have known this as of October 2012;  
19      is that correct?

20      A.       Yes.

21      Q.       You'd also agree with me, Dr. Parkinson, that by  
22      October 2012 a person of ordinary skill in the art would  
23      have known that one of the key systems involved in metabolic  
24      drug-drug interactions was the cytochrome P450 enzyme  
25      systems.

CROSS-EXAMINATION - DR. PARKINSON

1                   Isn't that correct?

2           A.       Yes.

3           Q.       And you would agree with me that by October 2012 a  
4           person of ordinary skill in the art would have known that  
5           79 percent of drugs that were cleared by the liver  
6           interacted with CYP3A4, CYP 2C9, CYP 2D6 and/or CYP 2C19;  
7           isn't that correct?

8           A.       I won't testify to the exact percentage but that high  
9           percentage has appeared in many, many review articles. I  
10          concede that those particular enzymes are very active in the  
11          metabolism of a large number of drugs.

12          Q.       Now, you would agree with me, Dr. Parkinson, that a  
13          person of ordinary skill in the art, they would have known  
14          by October 2012 that for small molecules like tasimelteon,  
15          CYP3A4 had been shown to metabolize those drugs in more than  
16          50 percent of the cases; isn't that correct?

17          A.       I'm sorry. Could you repeat the question.

18          Q.       Absolutely.

19                   Now, you would agree a person of ordinary skill  
20          in the art would have known by October 2012 for  
21          small-molecule drugs like tasimelteon, CYP3A4 had been shown  
22          to metabolize these drugs in more than 50 percent of the  
23          cases; isn't that correct?

24          A.       A large percentage. The number might change from  
25          review to review but it's in that neighborhood, yes.

CROSS-EXAMINATION - DR. PARKINSON

1 Q. But you would agree the CYP3A4 would metabolize these  
2 drugs in more than 50 percent of the cases? Do you agree  
3 with that?

4 A. I don't know about more than 50 percent of the cases,  
5 but it's a very, very large percentage of drugs. I concede  
6 that.

7 Q. And you agree with, Dr. Parkinson, that by  
8 October 2012 a person of ordinary skill in the art would  
9 have known CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and  
10 CYP3A4, those are enzymes that metabolize a very high  
11 percentage of small-molecule drugs.

12 Isn't that correct?

13 A. Yes.

14 Q. Now, if we go to JTX-95 in your binder.

15 MR. COBLENTZ: Mr. Brooks, can you put that up.

16 BY MR. COBLENTZ:

17 Q. And I believe you saw this -- probably saw this paper  
18 in Dr. Greenblatt's presentation. It's the Lynch paper.

19 A. Yes, I did.

20 Q. And if we look at the abstract at the very first  
21 sentence here, it says: Cytochrome P450 enzymes are  
22 essential for the metabolism of many medications.

23 Do you see that?

24 A. I do.

25 Q. And then it says: Although this class has more than



CROSS-EXAMINATION - DR. PARKINSON

1 50 enzymes, six of them metabolize 90 percent of the drugs,  
2 with the two most significant enzymes being CYP3A4 and  
3 CYP2D6.

4 Do you see that?

5 A. I do.

6 Q. Now, you would agree with me, Dr. Parkinson, that the  
7 FDA guidance that was looked at in Dr. Greenblatt's  
8 presentation, that it recommended testing drug-drug  
9 interactions with seven different CYP enzymes, two of those  
10 were CYP1A2 and CYP3A4; is that correct?

11 A. Correct.

12 Q. And you would agree with me, Dr. Parkinson, that by  
13 testing the drug interactions with these drug-drug  
14 interactions, with these seven CYP enzymes, you capture  
15 98 percent of drugs; is that correct?

16 A. You would run those types of experiments with the  
17 vast majority, if perhaps all, small drug molecules, yes.

18 Q. Now, you would agree with me, by October 2012 that a  
19 person of ordinary skill in the art, they would have known  
20 that rifampicin was a strong CYP3A4 inducer?

21 Is that correct?

22 A. That was known, yes.

23 Q. And it was known by October 2012 that rifampicin was  
24 a strong inducer of CYP1A2, correct?

25 A. You mean an inducer of CYP3A4?

CROSS-EXAMINATION - DR. PARKINSON

1 Q. It was also an inducer of CYP1A2; is that correct?

2 A. There are some reports on CYP1A2.

3 Q. And you would agree with me that by October 2012 a  
4 person of ordinary skill in the art, they would have known  
5 that fluvoxamine, Cipro, they were strong CYP1A2 inhibitors;  
6 is that correct?

7 A. Yes.

8 Q. If you could look in your binder, DTX-9.

9 Mr. Brooks, if you could put DTX-9 up on the  
10 screen.

11 A. Yes.

12 Q. Now, this is the Badyal paper that Dr. Greenblatt  
13 discussed?

14 Did you hear him discuss this paper?

15 A. I did.

16 Q. And if we go to DTX-9.7. And --

17 A. I'm sorry. What page are you on?

18 Q. You see at the bottom, DTX and it says "dash"?

19 A. 9 --

20 Q. We're going to go to DTX-9.7.

21 A. 9.7, yes.

22 Q. Are you there?

23 A. Yes, sorry.

24 Q. And so if we're on the left-hand column, we see a  
25 heading "Prediction of Interactions."

CROSS-EXAMINATION - DR. PARKINSON

1 Do you see that?

2 A. Yes, I do.

3 Q. And under that it says: The prediction of  
4 inhibition-based interactions has been possible for new drug  
5 candidates as a result of identification of CYP isoenzymes  
6 and an increased awareness of their in-vitro and in vivo  
7 behavior.

8 Do you see that?

9 A. Yes, I do.

10 Q. And the next sentence says: For any new drug the  
11 spectrum of drug interactions can be predicted even before  
12 the drug reaches the clinical phase of the development.

13 Do you see that?

14 A. I do.

15 MR. COBLENTZ: Pull that down.

16 BY MR. COBLENTZ:

17 Q. Now, if you could turn to JTX-92 in your binder.

18 A. Yes.

19 Q. And this is a paper by Dr. Obach?

20 A. Yes.

21 Q. You see that?

22 And it's entitled "Metabolism of ramelteon in  
23 human liver microsomes and correlation with the effect of  
24 fluvoxamine on ramelteon pharmacokinetics."

25 A. I agree with that, yes.

CROSS-EXAMINATION - DR. PARKINSON

1 Q. And you considered this reference?

2 A. I did.

3 MR. COBLENTZ: I'd like to offer JTX-92 into  
4 evidence.

5 MR. KLEIN: No objection.

6 THE COURT: All right. It's admitted.

7 (JTX-92 admitted into evidence.)

8 BY MR. COBLENTZ:

9 Q. Now, if we go to the introduction at the bottom of  
10 the left-hand column and over to the right-hand column,  
11 you'll see here it says: "The reference states among the  
12 large number of drugs available, there is a small subset  
13 well established as perpetrators of DDIs known to cause  
14 large (i.e., greater than five-fold) increases in exposure  
15 to other drugs."

16 Do you see that?

17 A. Yes, I do.

18 Q. And Dr. Parkinson, you would agree with me that part  
19 of this small set of DDIs mentioned here, fluvoxamine would  
20 have been one of those; is that correct?

21 A. Yes.

22 Q. And rifampicin, that would have been considered one  
23 of these perpetrators of DDIs mentioned here; is that  
24 correct?

25 A. Technically, no, but because what rifampicin does is

CROSS-EXAMINATION - DR. PARKINSON

1       cause more than a five-fold increase in clearance, not  
2       exposure.

3       Q.       So it would not have been one of the perpetrators of  
4       DDIs?

5       A.       Well, it's a perpetrator of DDI but it causes a  
6       five-fold decrease in exposure, not a five-fold increase.

7       Q.       I take your point.

8               Now, if we go to the discussion of this  
9       publication on Page 10.

10      A.       That's the JTX-10.

11      Q.       Yeah, JTX -- I believe 92.

12      A.       10 and 11, yes.

13      Q.       And it's Page 10?

14      A.       Yeah.

15      Q.       And we see there's a section here called  
16      "Discussion."

17               Do you see that?

18      A.       Yes, I do.

19      Q.       And it says here that: It's highly desirable to be  
20      able to quantitatively predict DDI from in-vitro inhibition  
21      data.

22               Do you see that?

23      A.       Yes, I do.

24      Q.       And it says: Such data are routinely gathered during  
25      research on new drugs and in general have been successfully

CROSS-EXAMINATION - DR. PARKINSON

1 leveraged -- let me start over because I really butchered  
2 that.

3 It says: It is highly desirable to be able to  
4 quantitatively predict DDI from in-vitro inhibition data.

5 Do you see that?

6 A. Yes.

7 Q. And then it says: Such data are routinely gathered  
8 during research on new drugs and in general have been  
9 successfully leveraged to predict DDI.

10 Do you see that?

11 A. I do.

12 Q. Now I'd like to go back to JTX-95. And this is back  
13 to the Lynch paper. And if we could go to page 2 of this  
14 publication. There's a table there at the top.

15 A. Yes.

16 Q. And it says: Key recommendations for practice.

17 Do you see that?

18 A. Yes.

19 Q. And then the last one here, do you see where I'm at?  
20 It says: "Because they are known..."

21 And it says: "Because they are known to cause  
22 clinically significant P450 drug interactions, always use  
23 caution when adding the following substances to medications  
24 that patients are taking."

25 Do you see that?

CROSS-EXAMINATION - DR. PARKINSON

1 A. Yes.

2 Q. And it mentions antidepressants and anti-tubercular  
3 drugs.

4 Do you see that?

5 A. I do.

6 Q. Is fluvoxamine considered an antidepressant?

7 A. Yes.

8 Q. And rifampicin, that would be an anti-tubercular  
9 drug?

10 A. Yes.

11 Q. Now, quickly, I just want to look at PTX-393. I  
12 believe you testified to this on your direct. I just wanted  
13 to clear something up here because it was mentioned that  
14 ketoconazole is a cream.

15 In this particular study, if we look at the  
16 introduction, it was looking at the oral antifungal agent;  
17 is that correct?

18 A. Yes.

19 Q. I just wanted to clear that up for the record.

20 THE COURT: The reason why I asked is because I  
21 thought his background was in psychiatric and other areas.  
22 And I thought, because I have had other cases, believe it or  
23 not, involving ANDAs and other drugs and I'm like it just  
24 didn't seem to fit the mold.

25 So for both sides, don't worry. I'm not drawing

CROSS-EXAMINATION - DR. PARKINSON

1 any conclusions. It was just curiosity.

2 MR. COBLENTZ: I just wanted to make sure it was  
3 clear for the record --

4 THE COURT: I'm not making any findings relative  
5 ketoconazole.

6 BY MR. COBLENTZ:

7 Q. Now, Dr. Parkinson, you would agree with me none of  
8 the asserted patent claims of the asserted patents refer to  
9 the magnitude of drug-drug interactions between tasimelteon  
10 and a CYP1A2 inhibitor; isn't that correct?

11 A. That information is contained within the patent, and  
12 the claims that call for a -- not to coadminister the two  
13 drugs is based on the actual magnitude of the drug-drug  
14 interaction.

15 Q. But the actual language about the magnitude of the  
16 drug-drug interaction with the CYP1A2 inhibitor, that's not  
17 in the claim language; is that correct?

18 A. In the claim language, no.

19 Q. Now, you would agree with me that none of the  
20 asserted patent claims of the asserted patents mention the  
21 magnitude of drug-drug interaction between tasimelteon and  
22 CYP3A4 inducer; isn't that correct?

23 A. They don't specify the magnitude, but the mere fact  
24 they are calling that the drugs not to be coadministered  
25 indicates that the magnitude was clinically significant.



CROSS-EXAMINATION - DR. PARKINSON

1 Q. Now, you'd agree with me, Dr. Parkinson, by  
2 October 2012 a person of ordinary skill in the art, they  
3 would have known that melatonin was metabolized by CYP1A2;  
4 is that correct?

5 A. That was in the public domain, yes.

6 Q. And you would agree with me that a person of ordinary  
7 skill in the art, they would have known by October 2012 that  
8 ramelteon was metabolized by CYP1A2 and CYP3A4; is that  
9 correct?

10 A. That was also in the public domain, yes.

11 MR. COBLENTZ: Now, Mr. Brooks, if you could  
12 pull up Table 1 on Page 43 of the Parkinson rebuttal report.

13 BY MR. COBLENTZ:

14 Q. Now, I'm going to do my best with these names, so  
15 bear with me.

16 You would agree with me tasimelteon and  
17 ramelteon share a dihydrobenzofuran structure; is that  
18 correct?

19 A. Yes, they do.

20 Q. And you would agree with me that tasimelteon and  
21 ramelteon, they have the same number of heteroatoms; is that  
22 correct?

23 MR. KLEIN: Objection, Your Honor. I don't  
24 believe I went near this subject matter in my direct  
25 examination.

CROSS-EXAMINATION - DR. PARKINSON

1 MR. COBLENTZ: You did -- you don't --

2 MR. KLEIN: Did I?

3 THE COURT: Well, hold on.

4 I don't recall that.

5 MR. COBLENTZ: No. Well, we -- did you not  
6 discuss ramelteon in your --

7 (Discussion held off the record.)

8 THE COURT: You talked about structural  
9 similarity which is what it seems like you're getting to.

10 MR. COBLENTZ: I am. But he did discuss  
11 ramelteon --

12 THE COURT: I'll let it go for a little bit.  
13 Again, cognizant of time, but I'll let it go a little bit.  
14 BY MR. COBLENTZ:

15 Q. And both ramelteon and -- well, both ramelteon and  
16 tasimelteon, they have two oxygen atoms and one nitrogen  
17 atom; is that correct?

18 A. Correct.

19 Q. And they have the same number of ring systems; is  
20 that correct?

21 A. Different ring systems, the same total number.

22 Q. Now, both tasimelteon and ramelteon, they work  
23 through the MT-1 and MT-2 receptors; is that correct?

24 A. Before I answer that, you have deliberately omitted  
25 anything about the chiral centers. You are asking --

CROSS-EXAMINATION - DR. PARKINSON

1 Q. And you can answer that question --

2 THE COURT: Now, see, this is why -- I'm going  
3 to sustain the objection because see, now we're all trying  
4 stuff. You went beyond the scope of cross, and that's  
5 precisely why we shouldn't be doing it.

6 So I'm going to sustain the objection. There  
7 were no questions. Unless you want to remind me and point  
8 me to the transcript, I recall no questions about the  
9 structure of these two substances.

10 Now is your chance, let me know.

11 MR. COBLENTZ: Yeah, I'll move on.

12 THE COURT: All right. Then it's beyond the  
13 scope.

14 MR. KLEIN: Your Honor, I move to strike the  
15 testimony and the question.

16 THE COURT: Well, you've got some good answers  
17 there. You know what, I'll strike it all at this point.  
18 It's fine. It's not going to make any difference.

19 BY MR. COBLENTZ:

20 Q. Now we go to JTX-130, and this is the FDA guidance  
21 concerning interaction studies.

22 Do you see that?

23 A. It's the 2012 FDA guidance on drug interactions.

24 Q. And if we go to Page 6 and we look at the bullet that  
25 says, The study of drug-drug interactions, do you see that?

CROSS-EXAMINATION - DR. PARKINSON

1                   And it says: The study of drug-drug  
2 interactions for a new drug generally begins with in-vitro  
3 studies to determine whether a drug is a substrate inhibitor  
4 or inducer of metabolizing enzymes.

5                   Do you see that?

6           A.       I do.

7           Q.       And then it says here that: The results of in-vitro  
8 studies will inform the nature and extent of in vivo studies  
9 that may be required to assess potential interactions.

10                   Is that correct?

11          A.       Correct.

12          Q.       And these are the FDA draft guidance from February of  
13 2012; is that correct?

14          A.       It is.

15          Q.       All right.

16                   MR. COBLENTZ: If we could pull up JTX-150.

17                   If you go there in your binder.

18                   THE WITNESS: Yes.

19          BY MR. COBLENTZ:

20          Q.       Now, JTX-150, this is a paper by a Dr. Ogilvie.

21                   Do you see that?

22          A.       I do.

23          Q.       And it's: The Clinical Assessment of Drug-Drug  
24 Interactions of Tasimelteon, a Novel Dual-Melatonin Receptor  
25 Agonist?

CROSS-EXAMINATION - DR. PARKINSON

1 A. Yes, that is the title of the paper.

2 Q. And if we turn to -- if we turn to Page 7, we see  
3 there is a declaration of conflicting interest.

4 Do you see that?

5 And it says here that: These studies described  
6 were funded by Vanda Pharmaceuticals.

7 Do you see that?

8 A. Yes.

9 Q. Now, I'd like to go to Page 2 of JTX-150. And if we  
10 look at the first full paragraph in the left-hand column,  
11 here it states: Early in-vitro studies suggested that  
12 cytochrome P450, CYP1A1, CYP1A2, CYP2C9, and CYP2D6 were the  
13 mayor CYP enzymes involved in the metabolism of tasimelteon  
14 with some contributions by CYP2C19.

15 Do you see that?

16 A. I see that.

17 Q. And it cites a reference number 14.

18 Do you see that?

19 A. I do.

20 Q. And if we go to the last page of this document, which  
21 is Page 8, citation 14 is the Vachharajani reference.

22 Do you see that?

23 A. I do.

24 Q. Now, I want to go back to Page 2 of this document.

25 And if we look at the sentence that -- after the one I just

CROSS-EXAMINATION - DR. PARKINSON

1 read, it says: Additional in-vitro studies suggested that  
2 CYP1A2 and CYP3A4/5 are the major CYP enzymes involved in  
3 the metabolism of tasimelteon with minor involvement of  
4 CYP2C9, CYP2C19, and CYP2D6 in the formation of the most  
5 abundant metabolites, including M9, M11, M12, M13, and M14.

6 Do you see that?

7 A. I do, followed by the citation 13.

8 Q. Right.

9 And if we go over to the right-hand column of  
10 this page, on Page 2, we see here there's a sentence that  
11 says: Because CYP1A2 --

12 Do you see where I'm at?

13 A. Yes.

14 Q. It says: Because CYP1A2 and CYP3A4/5 appeared to be  
15 prominently involved in the metabolism of tasimelteon,  
16 clinical studies were conducted to examine the effects of  
17 strong inhibition (fluvoxamine) and moderate induction  
18 (cigarette smoking) of CYP1A2, and strong inhibition  
19 (ketoconazole) and induction (rifampin) of CYP3A4/5.

20 Do you see that?

21 A. I do.

22 MR. COBLENTZ: I have nothing further.

23 THE COURT: All right. Any redirect?

24 MR. KLEIN: Just one -- one or two questions,

25 Your Honor.

DIRECT EXAMINATION - DR. CZEISLER

1 MR. COBLENTZ: I have been reminded I need to  
2 offer JTX-150 into evidence.

3 MR. KLEIN: No objection, Your Honor.

4 And no redirect.

5 THE COURT: All right. It's admitted.

6 (JTX-150 admitted into evidence.)

7 THE COURT: May I ask you, sir, because I asked  
8 the last witness. Have you testified before?

9 THE WITNESS: Last November.

10 THE COURT: And before that?

11 THE WITNESS: Never.

12 THE COURT: All right. How did you like it?

13 THE WITNESS: Kind of stressful.

14 THE COURT: All right. Thank you very much.

15 You're excused.

16 THE WITNESS: Thank you, sir.

17 (Witness excused.)

18 THE COURT: Next?

19 MR. GROOMBRIDGE: Vanda's next and final witness  
20 is Dr. Charles Czeisler.

21 CHARLES CZEISLER, having been called as a  
22 witness, testified as follows:

23 DIRECT EXAMINATION

24 MR. GROOMBRIDGE: Your Honor, pursuant to the  
25 parties' stipulation, we are presenting Dr. Czeisler as an

DIRECT EXAMINATION - DR. CZEISLER

1 expert in circadian rhythms and sleep and circadian rhythm  
2 disorders, including Non-24.

3 MR. ROZENDAAL: No objection.

4 THE COURT: All right.

5 BY MR. GROOMBRIDGE:

6 Q. Now, could you just introduce yourself to the Court,  
7 please, Dr. Czeisler.

8 A. Yes, my name is Dr. Charles Czeisler. I am the chief  
9 of the Division of Sleep and Circadian Disorders at the  
10 Brigham and Women's Hospital and the Baldino Professor of  
11 Sleep Medicine at the Harvard Medical School where I direct  
12 the Division of Sleep Medicine.

13 Q. Could you please briefly describe your educational  
14 background?

15 A. I graduated from Harvard College in molecular biology  
16 and biochemistry in 1974, and then I went to Stanford  
17 Medical School where I received a PhD in neurosciences and  
18 an MD degree in 1981.

19 Q. And did you do any postdoctoral training?

20 A. Yes. I was a senior fellow in health policy at the  
21 Harvard Institute School of Government for two years  
22 following my MD.

23 Q. What does your research focus on?

24 A. My research focuses on the neurobiology of the human  
25 circadian pacemaker and its resetting, and the application



DIRECT EXAMINATION - DR. CZEISLER

1 of those findings to the diagnosis and treatment of  
2 circadian rhythm sleep disorders and to occupational  
3 medicine.

4 Q. And, Doctor, you have been sitting in the courtroom  
5 for the past few days, correct?

6 A. Yes, I have.

7 Q. Now, having heard a fair amount of the subject matter  
8 of the trial, is there any aspect of your work over your  
9 career that you feel is particularly relevant to the issues  
10 in this case?

11 A. Yes. One of the things that -- one of the  
12 discoveries that I made in the course of my career is  
13 discovering that light was the primary resetting stimulus  
14 for human circadian pacemaker. We were the first to show  
15 that light could reset the internal clock in humans.

16 And one of the other things that I did was  
17 49 years ago began working on Non-24-Hour disorder in a  
18 sighted person, actually, and published that paper in 1978,  
19 and then began doing subsequent studies. And we were the  
20 first to describe an individual whose sleep was restricted  
21 only to the nighttime hours, who was blind, he was a high  
22 school teacher, and nonetheless, his daily sleep period was  
23 processing around and around the clock.

24 And it was quite a surprise to us at that time  
25 because we thought, like in sighted people, that the actual

DIRECT EXAMINATION - DR. CZEISLER

1 sleep times would be moving around and around the clock.  
2 But people who are constrained to working during the day and  
3 sleeping at night, they don't have the luxury. Just like if  
4 you were to travel to Japan, your daily sleep period would  
5 remain here in Wilmington even though you're trying to  
6 function in Tokyo and try to sleep during the night there  
7 and try to stay awake during the day there.

8 Q. Now, Doctor --

9 MR. ROZENDAAL: Your Honor, may the witness be  
10 asked to keep his voice up. I'm having difficulty hearing  
11 him.

12 THE WITNESS: I will do my best.

13 THE COURT: We can turn it up a little bit for  
14 you. Okay.

15 BY MR. GROOMBRIDGE:

16 Q. Doctor, your finding with respect to light that reset  
17 the circadian rhythm, did that receive any attention in the  
18 wider world?

19 A. It did. It was on the cover of Science and the front  
20 page of the New York Times.

21 Q. Now, Doctor, you, by the way, I think in that answer  
22 mentioned daily sleep period. Are you familiar that that's  
23 a term that has been the subject of testimony in the trial?

24 A. I am.

25 Q. And in forming your opinions, have you -- or I should

DIRECT EXAMINATION - DR. CZEISLER

1 ask, what have you -- what understanding of that term have  
2 you used as you form your opinions that you're about to  
3 give?

4 A. The understanding of that term is that it refers to  
5 the phase of the circadian cycle at which we are able to  
6 maintain consolidated sleep, and I have prepared a few  
7 slides to illustrate that.

8 Q. I would like to go -- in the interest of time, let's  
9 see how we go -- well, let's try that.

10 MR. GROOMBRIDGE: Let's bring up the -- let's go  
11 to Slide 6, please.

12 Move on forward, please, Mr. Weir, to  
13 Slide 11.6.

14 No, back one. That's it.

15 BY MR. GROOMBRIDGE:

16 Q. And could you just please explain here how you're  
17 using the term "daily sleep period" and why?

18 A. The daily sleep period is this 7-to-9 hour interval  
19 during which an individual is able to maintain consolidated  
20 sleep. It's often difficult to sleep outside of that  
21 interval when we try to do so, as night shift workers need  
22 to do when they stay awake at night and try to sleep during  
23 the day. And it's also difficult to stay awake if you're  
24 trying to stay awake during the daily sleep period, as we  
25 sometimes do in preparing for a trial I have seen this week,

DIRECT EXAMINATION - DR. CZEISLER

1 actually, among the lawyers.

2 Sighted humans often try to override this  
3 biological timing in order to do whatever they have to do.  
4 Blind individuals, unfortunately, they are trying to sleep  
5 at night and be awake during the daytime so that they can  
6 fit into society and have jobs and do their work.

7 But their daily sleep period is processing  
8 around and around without their ability to control. And  
9 that's the fundamental neurobiology of Non-24 disorder.

10 Q. What is the daily sleep period in healthy people?

11 A. Well, I'm going to use the slide that Dr. Emens used  
12 in his report. In normal, healthy people, the average daily  
13 sleep period is occurring during, in this example, from,  
14 let's say, 11:00 p.m. to 7:00 a.m. There are individual  
15 differences. There are morning types and evening types and  
16 so on.

17 But Dr. Emens illustrated in the case of -- and  
18 I have illustrated the daily sleep, the normal time of when  
19 we sleep is between, let's say, 11:00 p.m. and 7:00 a.m.  
20 But in these circadian rhythm sleep disorders, like  
21 advanced -- sleep-wake advance phase disorder, patients with  
22 that disorder, their daily sleep period is starting, let's  
23 say, at 7:00 p.m. in the evening, but that's when their  
24 families are around, they're home from work. Most of them  
25 can't actually sleep during the beginning of the advanced

DIRECT EXAMINATION - DR. CZEISLER

1 sleep period, and so they end up staying up until, let's  
2 say, 11:00 in the evening and then they wake up at 3 o'clock  
3 in the morning because their internal clock wakes them up  
4 because their daily sleep period has ended even though they  
5 just started to sleep.

6 Patients with delayed sleep-wake phase disorder  
7 have the opposite situation, as Dr. Emens has illustrated  
8 here. They can't fall asleep until 4:00 or 5:00 in the  
9 morning because their daily sleep period doesn't start until  
10 then. And then if they have to wake up for classes or wake  
11 up for work, they end up having to interrupt their daily  
12 sleep period to try to function during the usual daytime  
13 hours.

14 For the blind people with Non-24 disorder, their  
15 daily sleep period is processing around and around the  
16 clock.

17 Q. Now, there's been some discussion of so-called phase  
18 response curves, Doctor, and specifically phase response  
19 curves for melatonin.

20 Are you familiar with those?

21 A. Yes, I am.

22 Q. And did the understanding in the art as to the phase  
23 response curve for melatonin evolve over time?

24 A. It did.

25 Q. And I would like to look at where it was.

DIRECT EXAMINATION - DR. CZEISLER

1 Do you have in front of you a white binder of  
2 exhibits?

3 A. Yes, I do.

4 Q. And could we just -- I forgot to do this, but could  
5 we start with the first one you should find there, PTX-824.

6 A. Yes.

7 Q. Now is that your curriculum vitae?

8 A. It is.

9 MR. GROOMBRIDGE: Your Honor, we offer  
10 Plaintiff's Exhibit 824.

11 MR. ROZENDAAL: No objection.

12 THE COURT: It's admitted.

13 (PTX-824 admitted into evidence.)

14 BY MR. GROOMBRIDGE:

15 Q. And now, Dr. Czeisler, if you could turn on -- I  
16 think it's two more items and you hopefully will find  
17 JTX-127.

18 A. Yes.

19 Q. What is this?

20 A. This is a study that was published in 2010 by  
21 Dr. Burgess and colleagues and in Dr. Eastman's laboratory.

22 Q. And have you used -- relied on this in part in  
23 forming your opinions in this case?

24 A. Yes, I have.

25 MR. GROOMBRIDGE: Your Honor, we offer JTX-127.

DIRECT EXAMINATION - DR. CZEISLER

1 MR. ROZENDAAL: No objection.

2 THE COURT: It's admitted.

3 (JTX-127 admitted into evidence.)

4 MR. GROOMBRIDGE: And let's move on, please, if  
5 we can on the screen to PDX-11.13.

6 BY MR. GROOMBRIDGE:

7 Q. Now, Dr. Czeisler, what are we looking at here?

8 A. Here, we're looking at an excerpt from that article  
9 which shows the phase response curve to light -- excuse me,  
10 to melatonin.

11 The interesting thing about this particular  
12 phase response curve to melatonin is that the previous phase  
13 response curves were conducted in sighted participants who  
14 were not shielded from the 24-hour light/dark cycle. They  
15 were actually living in an environment outside of the  
16 laboratory and getting the melatonin capsules at specific  
17 times of day. So the light/dark cycle, which is the most  
18 powerful synchronizing phase in humans, was imposing the  
19 impact of melatonin in prior PRCs.

20 So what was important about Dr. Burgess's 2008  
21 and 2010 article, both of which I summarized here, is the  
22 shape of the new PRC to melatonin that she identified. And  
23 this was done in very dim light and near darkness, and  
24 individuals were put on a very unusual sleep-wake schedule  
25 so that they could be administered the melatonin without

DIRECT EXAMINATION - DR. CZEISLER

1       disturbing and compare it to placebo.

2               So this is really the true phase response curve  
3       to melatonin without the influence of light and most  
4       applicable to blind people because these individuals were  
5       free-running or not entrained during the course of the  
6       experiment.

7       Q.       And did others in the field, including Dr. Emens,  
8       then begin to use this phase response curve?

9       A.       Yes. This was -- this was by -- people skilled in  
10      the art, including Dr. Emens, embraced as the more accurate  
11      phase response curve to melatonin.

12      Q.       Let me ask you to turn in the binder to the next  
13      item.

14               Is that a paper published by Dr. Emens and  
15      Dr. Burgess in 2015?

16      A.       Yes, it is.

17      Q.       And in that paper -- that's and JTX-145, correct?

18      A.       Yes.

19      Q.       And you also used this as part of the basis for your  
20      opinions here?

21      A.       Yes, I did.

22               MR. GROOMBRIDGE: And plaintiff's offer JTX-145,  
23      Your Honor.

24               MR. ROZENDAAL: No objection, Your Honor.

25               THE COURT: All right. It's admitted.



DIRECT EXAMINATION - DR. CZEISLER

1 (JTX-145 admitted into evidence.)

2 THE COURT: Mr. Groombridge, could you just hold  
3 up a second.

4 MR. GROOMBRIDGE: Yes.

5 THE COURT: Okay. Thank you.

6 MR. GROOMBRIDGE: Let's go to the next slide,  
7 please, Slide 14.

8 BY MR. GROOMBRIDGE:

9 Q. Dr. Czeisler, in this slide, have you indicated that  
10 phase response curve as it's depicted in Dr. Emens' 2015  
11 paper?

12 A. Yes, I have. And you'll notice several aspects of it  
13 are different than previously shown phase response curves.

14 First of all, it has a -- the part of the  
15 curve -- this is the peak time of phase advancing to an  
16 earlier hour. And the phase delays in response to  
17 melatonin, the crossover point, instead of beginning at  
18 1 o'clock, one hour after the usual bedtime, they're  
19 beginning two hours; the delays begin two hours before the  
20 usual bedtime. And the magnitudes of the responses are also  
21 higher.

22 Q. And did you depict on this, by way of a  
23 demonstrative, information about what the art taught  
24 regarding administration of melatonin?

25 A. Yes.

DIRECT EXAMINATION - DR. CZEISLER

1 Q. And can we show those.

2 What's the first one that we're look at here  
3 shown by the blue arrow labeled 1?

4 A. The blue arrow shows when the Lockley article, the  
5 first one showing a phase response -- showing entrainment  
6 with melatonin in some people who are given melatonin, gave  
7 it at 9:00 p.m. about two hours before the daily sleep  
8 episode.

9 Then the Sack study, twice as much melatonin was  
10 given at this particular point on the phase response curve  
11 in that New England Journal paper.

12 The Lewy study tested 0.5 milligrams taken at  
13 about 8:00 p.m.

14 The Hack study investigated 0.5 milligrams taken  
15 at 9:00 p.m., and the size of the arrows here are a cartoon  
16 illustration for differing amounts.

17 And then in 2017, Dr. Emens recommended, based  
18 on this phase response curve, taking low doses of melatonin  
19 six hours before bedtime, which was the consensus of people  
20 of extraordinary skill in the art, such as Dr. Emens, take  
21 away from this phase -- this new phase response curve  
22 that -- this set of phase response curves that were  
23 developed in 2008 and 2010.

24 Q. So let's focus just on the date of January 2012  
25 because that has significance in the case. What, in your

DIRECT EXAMINATION - DR. CZEISLER

1 opinion, would have been the conventional wisdom as to when  
2 melatonin should be administered in order to treat Non-24?

3 A. The consensus opinion as of that date would have been  
4 that melatonin should be administered approximately five to  
5 six hours before the desired bedtime. And this was  
6 expressed at many meetings and at -- in many -- by experts  
7 who I knew at the time.

8 Q. I'd like to turn to the so-called Rajaratnam paper.  
9 And were you in the courtroom yesterday when Dr. Emens  
10 discussed that?

11 A. Yes, I was.

12 Q. Do you agree with what he said?

13 A. I have great respect and admiration for Dr. Emens,  
14 but I don't agree with him on this particular point.

15 Q. And what is it about the Rajaratnam paper on which  
16 you differ?

17 Would it be helpful -- would you like to look  
18 at --

19 A. It would be helpful to have an illustration, but I  
20 can also describe the main point.

21 So the issue really is whether or not the study  
22 in the Rajaratnam included this spillover effect. We heard  
23 a lot about spillover yesterday, which involves, unlike  
24 light, if you give a stimulus of light and you turn off the  
25 light, it doesn't continue to reset the circadian system

DIRECT EXAMINATION - DR. CZEISLER

1 after you've turned it off.

2 But with melatonin or tasimelteon, in this case,  
3 when you give the stimulus as was described by Dr. Lockley  
4 yesterday, it continues in the blood stream for whatever its  
5 half-life is. And at the time, tasimelteon was thought to  
6 have about a two-hour half-life as was discussed earlier  
7 today.

8 So the only dose that was shown to be effective  
9 for the resetting phase in the Rajaratnam was a  
10 100-milligram dose. That was given five and a half hours  
11 before the daily sleep period of those sighted subjects who  
12 were suddenly moved to an earlier clock hour to try to  
13 simulate insomnia.

14 Dr. Emens said yesterday in his testimony that  
15 the -- that the 1.7 hour -- 1.75-hour shift that was  
16 observed in -- phase advance shift that was observed in  
17 response to that 100-milligram dose, as compared to placebo,  
18 was net of the -- of the spillover effect. And I think the  
19 reason why he made this mistake is all the studies of  
20 melatonin, the resetting effect is assessed the next day.

21 So you give the stimulus on day one and then the  
22 next day, you find out where is the phase of melatonin.

23 And the reason why you don't find it out on the  
24 same day is because if you've taken melatonin, you can't  
25 find out when the onset of it is because it's in the

DIRECT EXAMINATION - DR. CZEISLER

1 bloodstream. So you can't find out what the onset of  
2 endogenous melatonin is as compared to the melatonin dose.

3 And in the case of tasimelteon, the assay does  
4 not cross-react between tasimelteon and melatonin. So  
5 therefore what Rajaratnam did was he assessed it on the same  
6 day. So it was given at five and a half hours before the  
7 usual bedtime, and then what they noticed was -- and then  
8 the melatonin on that very same day was assessed. And it  
9 rose 45 minutes after they gave the 100-milligram tablet of  
10 tasimelteon. So that was within 45 minutes of his  
11 administration.

12 And if you look at this graph, so they gave the  
13 tasimelteon here --

14 Q. Let me pause you. Let's move to slide 21, please.

15 A. Okay. They gave the tasimelteon here and then it  
16 began the -- the melatonin began rising immediately here.  
17 So 45 minutes after that. And so it had no opportunity for  
18 whatever spillover effect that this huge dose of  
19 100-milligrams of melatonin. So it would be around -- half  
20 of it would still be around --

21 THE COURT: Wait. It was dosage tasimelteon, I  
22 thought.

23 THE WITNESS: Tasimelteon, I'm sorry. Did I say  
24 melatonin? If I said it, I misspoke.

25 THE COURT: All right.

DIRECT EXAMINATION - DR. CZEISLER

1 THE WITNESS: This huge dose of tasimelteon of  
2 100-fold milligrams, the melatonin then rose 45 minutes  
3 after that. So first of all, it's not even clear that  
4 that's a phase shift because sometimes the drug can elicit a  
5 response without necessarily shifting phase.

6 So the real proper way of assessing that is a  
7 person skilled in the art would have known would be the next  
8 day.

9 But it was assessed 45 minutes after it was  
10 given, it started rising so that was -- because that was --  
11 that was more than -- that was 2.75 hours before it had  
12 risen the day before.

13 And so -- so the -- it's really not possible to  
14 find out if after a then-stimulated to the light portion of  
15 the phase response curve here, what the net phase shift  
16 would have been. And a person of ordinary skill in the  
17 art -- because one of the reasons why it was accepted into  
18 the Lancet is that this is one of the first times that it  
19 had ever been shown that taking a pill could reset the  
20 circadian system within minutes.

21 And that's why it was on the cover of Lancet  
22 saying if this would be terrific, you would take it on the  
23 airplane and you'd be in London time before the plane  
24 landed. And that's why it was on the cover and why  
25 footballers -- this would be a dream for them to be able to

DIRECT EXAMINATION - DR. CZEISLER

1 shift their circadian rhythm so rapidly.

2 But the Rajaratnam study did not report what  
3 happened the next day, and so we don't know if the shift was  
4 maintained or if the 100-milligram dose then stimulated the  
5 delay portion of the phase response curve. Because after  
6 2 hours you would have 50 milligrams circulating; after  
7 another 2 hours, you'd still have 25 milligrams circulating;  
8 another two hours it is 12-and-a-half milligrams  
9 circulating.

10 These half-lives only reduce it by half and  
11 started out at such a huge dose and it's five times more  
12 than the dose that was actually used in the entrainment  
13 trials.

14 THE COURT: All right. Before you go on, I  
15 just -- so this graph, this long curve or multiple curves,  
16 is chronological, right?

17 THE WITNESS: Yes, that's the time of day, yes.

18 THE COURT: All right. Now, but when you said  
19 you administer the drug, the 100-fold milligrams, let's say  
20 on day one.

21 THE WITNESS: Right.

22 THE COURT: When a patient presents herself to  
23 you on Day 1, have you already conducted tests so that you  
24 know when she's going to start this sleep cycle in the  
25 beginning of it?

DIRECT EXAMINATION - DR. CZEISLER

1 In other words, how do you tell -- it is one  
2 thing to put the one, the arrow there, after the fact,  
3 right? But how do you get there at the very beginning?

4 THE WITNESS: Right. Well, these individuals  
5 have been -- have been recording their -- they had a  
6 sleep-wake history and they were required to maintain a  
7 regular schedule.

8 THE COURT: Before --

9 THE WITNESS: Before coming into the lab. And  
10 so that was established is that the habitual -- at that time  
11 habitual wake time of 11:00 p.m. to let's say 7:00 a.m., and  
12 then their habitual time, they were shifted; they were  
13 required to go to bed five hours earlier than their usual  
14 time. And they were administered the drug a half an hour  
15 before the new, newly required.

16 So it's just as if they flew on a supersonic jet  
17 to London and then --

18 THE COURT: These are people without the  
19 disorder?

20 THE WITNESS: Without the disorder.

21 THE COURT: Right. You've controlled it over a  
22 long period of time. You've established a regimented period  
23 when they fall asleep. And then you bring them in day one  
24 and you say now you're going to bed five hours earlier and  
25 we're going to administer the drug half an hour before that.



DIRECT EXAMINATION - DR. CZEISLER

1 THE WITNESS: And that's how Rajaratnam did it.

2 THE COURT: And that's how he can be confident.

3 All right.

4 BY MR. GROOMBRIDGE:

5 Q. Just on that point, Doctor, had any studies using  
6 tasimelteon been conducted in blind people before 2012?

7 A. No.

8 Q. Now, on this slide 21, you've marked with a 2, is  
9 that the timing and dosing that's set forth in the reissued  
10 patent?

11 A. Yes, it is.

12 Q. And that would be 20 milligrams of tasimelteon  
13 administered approximately one hour before target bedtime?

14 A. Yes.

15 Q. In your opinion, would that timing and dosage of  
16 administration have been obvious in January of 2012?

17 A. Absolutely not.

18 Q. Why not?

19 A. It wouldn't have been obvious because you're giving  
20 it in the -- after the onset, after the transition to the  
21 delay portion of the phase response curve. And in fact, I  
22 was around at the time and the investigative -- the  
23 investigator meeting and -- all the scientists and all the  
24 people who are of ordinary skill in the art, why are you  
25 giving it so late?

DIRECT EXAMINATION - DR. CZEISLER

1                   And in a dose that, you know, is below -- was  
2                   considered a high dose for tasimelteon, but it was not -- it  
3                   was one-fifth the dose that has been shown to have the phase  
4                   shifting effect.

5           Q.       And was this issue addressed at the so-called  
6                   advisory committee meeting about which the Court has heard?

7           A.       Yes.

8           Q.       Were you present at that meeting?

9           A.       Yes, I was.

10          Q.       And let me go, please, to the next slide. Let me go  
11                   to slide 22, please.

12                   And did Dr. Eastman ask a question about this?

13          A.       Yes.

14          Q.       What did she ask?

15          A.       She asked so this -- Dr. Eastman said so, this is  
16                   actually related to whether there's a PRC for tasimelteon,  
17                   because it was not known whether there was a PRC for  
18                   tasimelteon.

19                   But it's a simple question: Why did you pick  
20                   1 hour before bedtime for the drug administration?

21                   And then Dr. Polymeropoulos said that he was  
22                   aware of the literature and debating what is the right  
23                   timing of administration. And he said that we had to  
24                   balance two things, and one was to guess at what the PRC for  
25                   tasimelteon might be. So he's dealing -- he was dealing

DIRECT EXAMINATION - DR. CZEISLER

1 with insufficient evidence to make this decision. This was  
2 the creative part.

3 So the hope was that that would elicit a phase  
4 advance, but balancing the fact that since this drug has  
5 hypnotic effects. It's a soporific. Administering it  
6 5 hours before bedtime was considered impractical because  
7 you would make people so sleepy that they would not be able  
8 to interact with their families and others.

9 Their target bedtime was at 11:00 p.m. They  
10 didn't want to go to bed at 7:00 p.m. So that was the  
11 creative really element of this design.

12 Q. And by the way, there has been some testimony about  
13 the protocol for the SET and RESET trial as it appeared on  
14 clinicaltrials.gov.

15 Were you in the court for that?

16 A. Yes, I was. Well, not for the -- there was a whole  
17 discussion where I was sent outside because it was a  
18 question of whether that clinicaltrials.gov reference was  
19 going to be admitted.

20 Q. But you're familiar with the protocol itself?

21 A. Yes.

22 Q. In 2012, January of 2012, reading that protocol,  
23 would you have been surprised if the trial had failed?

24 A. Not at all.

25 Q. Why?

DIRECT EXAMINATION - DR. CZEISLER

1 A. I mean, I could have written a whole article about  
2 why it failed because it was given 1 hour before bedtime in  
3 someone where the target daily sleep episode, delay portion  
4 of the phase response curve was being stimulated. And so  
5 why would it elicit the desired phase advance. Because most  
6 blind people have an intrinsic period that is longer than  
7 24 hours and they need to be reset each day in an earlier  
8 direction.

9 Q. Doctor --

10 A. May I just elaborate on that answer.

11 Q. I'm sorry, I didn't mean to cut you off.

12 A. That's okay.

13 So if, instead -- what the circadian system will  
14 do if you give the drug repeatedly at that time is it will  
15 gradually delay until the advanced portion of the phase  
16 response curve hits it, as was described in yesterday's  
17 testimony.

18 But that would mean if that happened that the  
19 entire daily sleep episode would drift, let's say, so that  
20 you reach the optimal time that Dr. Emens recommended. That  
21 would mean that this would have to slip 6 or 7 hours meaning  
22 that the daily sleep episode of the blind person would be  
23 permanently at a misaligned phase so that it was -- so that  
24 was occurring during the daytime.

25 They would all have delayed sleep-wake phases so

DIRECT EXAMINATION - DR. CZEISLER

1     you've swapped one disorder for another. And so that could  
2     have been the outcome of this trial, and if it had been, if  
3     it had failed for that reason, it would not have been  
4     unexpected.

5     Q.     Are you familiar with the various prior art  
6     references that have been discussed in the courtroom, the  
7     '244 patent document, the Lankford paper and the Hardeland  
8     paper?

9     A.     Yes.

10    Q.     Is it your opinion that those by themselves or in  
11    combination would render the invention of the reissued  
12    patent obvious?

13    A.     No.

14    Q.     By the way, Doctor, do you have -- you're aware  
15    there's also a patent in the case that deals with  
16    administration without food?

17    A.     Yes, I am.

18    Q.     I'd like to talk very briefly about that. And maybe  
19    we could go to slide 39.

20                 Now, Doctor, have there been studies on  
21    circadian rhythm and the desire to eat?

22    A.     Yes.

23    Q.     And what, generally, have those studies shown?

24    A.     This particular study is the study of -- from one of  
25    the faculty members in our group. They've shown that the

DIRECT EXAMINATION - DR. CZEISLER

1 circadian drive for hunger actually peaks, unfortunately,  
2 late in the evening when it's the worst time for us to eat  
3 in terms of our metabolism.

4 And who knows their evolution how we got aligned  
5 in that particular way. But if we eat too close to the time  
6 that we release melatonin, melatonin helps keep blood sugar  
7 levels high in the night when we usually don't eat. So it  
8 does that by reducing the effectiveness of insulin.

9 So if we have, you know, a midnight snack, a  
10 bowl of ice cream or whatever, our insulin levels will go  
11 much higher once we have melatonin on board and this is  
12 thought to be contributing to the epidemic of diabetes that  
13 we have in the United States.

14 Q. And just, by the way, the study that you mentioned,  
15 is that the one that's been identified as PTX-513? If I  
16 look at the citation on this slide.

17 A. Yes.

18 MR. GROOMBRIDGE: Your Honor, plaintiff offers  
19 PTX-513.

20 MR. ROZENDAAL: No objection.

21 THE COURT: All right. It's admitted.

22 (PTX-513 admitted into evidence.)

23 THE WITNESS: In fact, one out of five people  
24 eat a full meal in the hour before they go to bed.

25 BY MR. GROOMBRIDGE:

DIRECT EXAMINATION - DR. CZEISLER

1 Q. I'd like to go now to slide -- well, let me -- let's  
2 try to cut that down.

3 In your opinion, Doctor, did the invention that  
4 we're talking about here, and specifically the use of  
5 tasimelteon to treat Non-24, did that meet a long felt but  
6 previously unmet medical need?

7 A. Absolutely.

8 Q. Why do you say that?

9 A. As I mentioned, I started working with the first  
10 patient with Non-24-hour disorder 49 years ago. And there  
11 were, you know, attempts to treat these individuals with  
12 melatonin, but there had been no large-scale clinical trial  
13 to find out if it were safe and efficacious. There were  
14 three people in that study and four people in that study,  
15 but no one had conducted an actual registration trial. And  
16 that's why there were no approved -- FDA approved treatment  
17 for this debilitating disorder.

18 I was at the FDA hearing, even though I had been  
19 working for decades in this area. And when I read and I  
20 knew how many blind people described the disability  
21 associated with Non-24 worse than the blindness itself which  
22 is hard for me to fathom.

23 But when I saw the people get up and testify,  
24 one of the blind individuals who couldn't even see the  
25 microphone as he was going up to do the testimony, he

DIRECT EXAMINATION - DR. CZEISLER

1 explained as a child when he was like seven he was living in  
2 a residential school for the blind. And he said the  
3 teachers were berating him for falling asleep in class and  
4 not -- you know, he should have been sleeping. And they  
5 would berate him if he were awake at night and he was making  
6 noise or whatever. And he just felt like he was a failure.

7 And then one of his teachers got up and she said  
8 I was -- I'm ashamed now, but I was one of the teachers who  
9 was berating children because -- who were blind because they  
10 weren't, you know, conforming to my idea of what a 24-hour  
11 day should be.

12 And I -- you know, as I said in my deposition, I  
13 was actually brought to tears listening to the people saying  
14 this, because it's just thinking about it. It's such a  
15 long-felt need. And to hear the individuals there  
16 explaining they had tried melatonin. It had not worked for  
17 them. They had tried it multiple times with different  
18 doctors. People who gave them psychiatric medication,  
19 people gave them a litany of different things to try to  
20 help.

21 Weight-promoting therapeutics and amphetamines.  
22 And they just could not -- many of them said that  
23 tasimelteon transformed their lives by being able to  
24 synchronize to the 24-hour day, so...

25 Q. One final thing I'd like to cover, Doctor.



DIRECT EXAMINATION - DR. CZEISLER

1 Are you aware -- and let's go, if we could, to  
2 slide 66.

3 Doctor, are you aware that with respect to the  
4 food effects patent, there is an assertion that it does not  
5 actually describe any benefit to taking tasimelteon without  
6 food?

7 A. Could I just have a moment to compose myself, I'm  
8 sorry.

9 (Pause.)

10 THE WITNESS: Okay.

11 BY GROOMBRIDGE:

12 Q. Actually, one of my colleagues points out that I  
13 omitted to ask something.

14 You're aware that there are two patents in this  
15 case that involve so-called drug-drug interaction?

16 A. Yes.

17 Q. And were you in the courtroom when Drs. Greenblatt  
18 and Parkinson testified this morning?

19 A. Yes.

20 Q. Having heard their testimony, is it -- do you have an  
21 opinion as to whether the claim of the patent involving  
22 drug-drug interaction with CYP1A2 substrates would or would  
23 not have been obvious?

24 A. That's not my area of expertise. I listened to both  
25 of their testimony. First, I found Dr. Greenblatt very

DIRECT EXAMINATION - DR. CZEISLER

1 compelling. Then I heard Dr. Parkinson and I found his --

2 Q. I'm not asking you to comment on their testimony.

3 I'm simply asking: Would the benefit of  
4 things --

5 A. Yes, with the benefit of them, I do not think it was  
6 obvious.

7 Q. And similarly, with respect to the patent involving  
8 drug-drug interaction around the CYP3A4 enzyme, do you have  
9 an opinion as to whether that would or would not have been  
10 obvious?

11 A. I do not think that that would have been obvious.

12 Q. And turning lastly to the food effect patent, is it  
13 your understanding that there is an assertion that this  
14 patent does not actually describe any benefit to taking  
15 tasimelteon without food?

16 A. Yes.

17 Q. And do you agree or disagree with that?

18 A. I disagree because the patent actually discloses the  
19 effect of food. It discloses -- this has to do with having  
20 a short sharp pulse. And so you administering it with food  
21 lowers the maximum concentration that it gets to and it  
22 lengthens the time that it takes to get to the Tmax.

23 And it incorporates by reference the RE604  
24 specification which actually explains that the ability to  
25 take tasimelteon an hour prior to sleep is advantageous

CROSS-EXAMINATION - DR. CZEISLER

1 because it allows for the avoidance of the soporific effects  
2 and the administration of a higher dose because it allows  
3 for the intervention in a different phase of the sleep  
4 cycle.

5 So it says without -- it appears that the  
6 ability to administer tasimelteon so close to sleep is a  
7 function of its Tmax, which is approximately a half an hour.  
8 So that's in the specification that you have this half an  
9 hour Tmax.

10 And the '487 patent says if you give it with  
11 food it's going to lengthen that Tmax. So I think that  
12 disclosure is in the '487 patent by reference to the RE604  
13 patent.

14 MR. GROOMBRIDGE: Thank you. That concludes my  
15 questions.

16 THE COURT: All right. Cross.

17 CROSS-EXAMINATION

18 BY MR. ROZENDAAL:

19 Q. Good afternoon, Dr. Czeisler. I'm J.C. Rozendaal.  
20 We have not yet met.

21 A. It's a pleasure to meet you.

22 Q. So, Dr. Czeisler, we've been talking about Non-24  
23 quite a bit for the last several days.

24 Is it fair to say that at least in the blind the  
25 defining characteristic of the condition is a lack of

CROSS-EXAMINATION - DR. CZEISLER

1       entrainment?

2       A.       I would agree.

3       Q.       Now, one of the asserted claims, Claim 3 of the  
4       reissued '604 patent, expressly talks about entraining a  
5       person to a 24-hour sleep-wake cycle; is that correct?

6       A.       Yes.

7       Q.       But there are other asserted claims that talk about  
8       treating patients with Non-24 that don't expressly mention  
9       entraining to a 24-hour sleep-wake cycle, correct?

10      A.       Could you please refer me to the patent.

11      Q.       Well, I can bring up an example of one. Let's see,  
12      how about -- oh, for example, Claim 14 of '829 patent, which  
13      is going to --

14      A.       Is that in my binder?

15      Q.       -- JTX-3, I think.

16      A.       Is that in my binder?

17      Q.       You know, I'm not sure if we have all the patents in  
18      the binder. I did not expect it to be a controversial  
19      point.

20                   MR. ROZENDAAL: Let's just -- you can just pull  
21      it up on the screen here.

22                   Claim 14. We're going to want 13 and 14  
23      together, I guess.

24      BY MR. ROZENDAAL:

25      Q.       So this is an example of the claim that talks about a

CROSS-EXAMINATION - DR. CZEISLER

1 method of treating a patient for a circadian rhythm disorder  
2 or sleep disorder, right? And then Claim 14 says the method  
3 of Claim 13, that comprises treating the patient for  
4 Non-24-Hour Sleep-Wake Disorder, right?

5 And so if we look at claims 13 and 14, we see a  
6 description of treating, but we don't see any express  
7 mention of the word entrainment, right?

8 A. Well, the goal of treating a patient for Non-24-hour  
9 disorder is entrainment, is synchronizing them to 24 -- it's  
10 converting them from having Non-24 to not having Non-24.  
11 That would be the goal of treatment. It's not always  
12 achieved but that's the goal.

13 Q. Right. So, that was the point I was trying to make.

14 So when you did your analysis of the claims,  
15 when you saw the word "treating" Non-24 sleep-wake disorder,  
16 that includes, in your mind, entraining or synchronizing the  
17 patient to a 24-hour sleep-wake cycle, right?

18 A. Well, not in all cases. I said it's the goal of the  
19 treatment.

20 Q. Well --

21 A. It certainly is not synonymous of treatment.

22 Q. Well, so, wait a minute, Doctor.

23 Did you -- did you not previously give a  
24 deposition in this case? Do you recall giving a deposition  
25 in this case?

CROSS-EXAMINATION - DR. CZEISLER

1 A. I did.

2 Q. You were, of course, under oath?

3 A. Yes.

4 Q. And --

5 A. I was asked this question -- I tried to count today  
6 when I reread my deposition. I think I was asked this  
7 question about eight or ten times during my deposition.

8 Q. Right. And you were asked --

9 A. Each time, except once, I said that it is the goal of  
10 treatment to synchronize someone. And on the last occasion  
11 when she asked me this question, I can't remember exactly  
12 what I said, but I think I said that -- I may have dropped  
13 the word "goal."

14 Q. Right. Didn't you, in fact, give testimony that when  
15 a claim only says treating and not synchronizing for  
16 entrainment, you read that as requiring entrainment or  
17 synchronizing? Didn't you say that?

18 A. The totality of my deposition did not say that it  
19 requires synchronization. I kept saying over and over again  
20 that it is the goal of treatment to synchronize but it is  
21 not synonymous with treatment.

22 Q. So your testimony today it's not synonymous of  
23 treatment. It is possible to treatment without entraining  
24 them?

25 A. Treatment doesn't always work. I don't know how to

CROSS-EXAMINATION - DR. CZEISLER

1 make this clear.

2 The goal of the treatment is to synchronize.

3 But, you know, if you look at the Vanda trial, not all the  
4 patients were synchronized, some were not synchronized. So  
5 they were treated but they were not synchronized.

6 In the first month, 20 percent of them were  
7 synchronized. Then, you know, with the extended treatment  
8 it got up to 59 percent. And then it got -- rose even  
9 higher.

10 But the goal of treatment in each case was to  
11 synchronize, but that doesn't mean it was always achieved.

12 I'm not sure what's unclear about that, but  
13 you're looking as if you're puzzled.

14 Q. I'm just trying to figure out, if I look at a claim  
15 like Claim 14 here. And I'm trying to figure out if that  
16 claim is being infringed, in order to demonstrate treating  
17 the patient for Non-24 sleep-wake disorder, do I need to  
18 demonstrate entrainment or do I not?

19 A. In order to demonstrate that the treatment was  
20 effective, it should entrain the circadian system.

21 Q. Right. But that was not my question, Doctor.

22 My question was, in order to practice this  
23 claim, in order -- in order to be practicing this claim,  
24 would a person -- and this goes to both infringement and  
25 invalidity, right, in order to have all the elements of this

CROSS-EXAMINATION - DR. CZEISLER

1 claim in the prior art, does one or does one not need to  
2 demonstrate entrainment in order to demonstrate treating a  
3 patient for Non-24?

4 A. Certainly the clinician practicing this claim would  
5 not have to demonstrate entrainment.

6 Q. So it's possible for a clinician to treat without  
7 entraining?

8 A. I didn't say that. You asked if the clinician would  
9 have to demonstrate that they have entrained the person,  
10 which would require taking 48-hour urine samples every two  
11 weeks. So no clinician is going to carry out the kind of  
12 study that Vanda did.

13 Q. So, Doctor, I'm not trying to make this unduly  
14 complicated. My point is that we have some claims that talk  
15 about treating that also expressly require entraining,  
16 right?

17 A. Can you show me such a claim?

18 Q. If we look at -- I believe it is Claim 3 of the RE604  
19 patent, which is JTX-1.

20 So if we look at, for example, the first -- the  
21 preamble to Claim 1, right?

22 A. Mm-hmm.

23 Q. It says: A method -- oh, sorry. It doesn't even say  
24 "treatment." It says a method of entraining.

25 So here we agree that if it were not possible to



CROSS-EXAMINATION - DR. CZEISLER

1 demonstrate entrainment, one would not be practicing this  
2 claim, right?

3 A. I think I'm not -- I'm not -- I think this is a  
4 special language that I'm perhaps not understanding, but  
5 this says a method of entraining. It doesn't say to me a  
6 method that requires the clinician to demonstrate that they  
7 have entrained the patient. It just says a method of  
8 entraining a patient suffering from Non-24 disorder, in  
9 which the patient awakens at or near a target wake time  
10 following a daily sleep period of approximately 7 to  
11 9 hours.

12 So that, to me -- and then it says: And  
13 maintaining said 24-hour sleep-wake cycle.

14 And then it says what the method comprises.  
15 Treating the patient orally with 20 milligrams of  
16 tasimelteon, taken once daily before target bedtime. It  
17 doesn't say anything to me about demonstrating the  
18 entrainment. It doesn't say you have to collect 48-hour  
19 urine samples every two weeks to demonstrate entrainment. I  
20 don't know --

21 Q. No, I'm not talking about -- no, I'm not saying one  
22 needs to --

23 A. You used the word "demonstrate." Do you have to  
24 demonstrate entrainment to practice the claim.

25 Q. Suppose I have a patient who is treated with the oral

CROSS-EXAMINATION - DR. CZEISLER

1 administration of 20 milligrams of tasimelteon once daily  
2 before bedtime, okay.

3 Are you with me so far?

4 A. I'm sorry, can you repeat that?

5 Q. Yes. Suppose that I have a patient --

6 A. Mm-hmm.

7 Q. -- who is being treated by the oral administration of  
8 20 milligrams of tasimelteon once daily before bedtime. All  
9 right?

10 And further assume that that patient does not  
11 entrain to a 24-hour sleep-wake cycle.

12 Still with me?

13 Have I or have I not practiced the claim, Claim  
14 1 here? I want to -- I need to get your understanding of  
15 what it means to practice this claim.

16 A. To practice this claim, it would be a method of  
17 entraining. So you would -- it would require that you  
18 entrain the individual, but it doesn't, in my view, require  
19 that you demonstrate that you have entrained the individual.

20 Q. Okay. Fine.

21 But there has to be an entrainment in order for  
22 this claim to be successful?

23 A. Yes. Yes. I agree with that.

24 Q. Now, my question is -- now my question is -- right.  
25 I didn't mean to get tripped up on demonstrating. I

CROSS-EXAMINATION - DR. CZEISLER

1 apologize.

2 Now, my question is for the claim we just looked  
3 at, which doesn't expressly mention entraining but just  
4 talked about treating a patient with Non-24, does satisfying  
5 that claim, which just talks about treating, also require  
6 entraining or not?

7 A. In that case, I would not think it would require  
8 entraining.

9 Q. All right. Now, in forming your opinions on  
10 obviousness in this case, you considered whether a person of  
11 ordinary skill in the art would have a reasonable  
12 expectation of success in achieving the claimed inventions,  
13 right?

14 A. Yes.

15 Q. Now, you would agree that FDA approval is not  
16 required to show a reasonable expectation of success.

17 A. No, it would not be required.

18 Q. And before FDA approval, sometimes clinical trials  
19 are carried out, right, and I think you've referred to those  
20 as registration trials.

21 Is that fair?

22 A. Yes.

23 Q. And we agree that a registration trial level of  
24 success is also not necessary to show a reasonable  
25 expectation of success in the context of obviousness.

CROSS-EXAMINATION - DR. CZEISLER

1 A. Yes.

2 Q. Okay. You mentioned spillover effects in your direct  
3 testimony. You're not aware of any study in the prior art,  
4 which is to say, before the 2012 priority date, that  
5 addresses spillover effects for tasimelteon, right?

6 A. Correct.

7 Q. All right.

8 I'd like to pull up, if we can -- and I think  
9 some slides were taken out of your slide deck and so I'm not  
10 sure if we have the numbers right. I'd like to try pulling  
11 up PDX-11.14.

12 And that's not it. Should we try 17?

13 And the next one, and the next one.

14 Here we go.

15 So PDX-11.17 that we see here on the screen is a  
16 phase response curve or a schematic of a phase response  
17 curve for melatonin, correct?

18 A. Yes, this was taken from the Emens 2015 article.

19 Q. That's what I want to establish.

20 The Emens 2015 article is not prior art, right?

21 A. That's correct, but this schematic is a reproduction  
22 of the 2010 article from Dr. Burgess.

23 Q. Right. And the 2010 article by Dr. Burgess was with  
24 data collected from sighted individuals, not people who were  
25 suffering from Non-24, right?

CROSS-EXAMINATION - DR. CZEISLER

1 A. Correct. But she was keeping them in near darkness  
2 so that they would free run as patients with Non-24 disorder  
3 do.

4 Q. Okay. And then on the right-hand side of PDX-17, you  
5 have a cite to an Emens 2017 article talking about the  
6 timing of melatonin administration.

7 That's also not prior art, right?

8 A. Melatonin and melatonin agonist, yes, that's also --  
9 that's correct.

10 Q. Not prior art, right? Just so that we're clear.  
11 Sorry.

12 A. Yes.

13 Q. All right. Now, we can try PDX-11.21. No, that's  
14 also -- that's not it. 25, perhaps? There we go.

15 So now 11.25 is the same schematic, right? And  
16 you were making the point that the timing of the  
17 administration would not necessarily have been obvious  
18 because it might have the effect of delaying rather than  
19 advancing the phase shift; is that correct?

20 A. Correct.

21 Q. All right. So just so that we all understand what's  
22 going on here, because I think this is kind of an important  
23 point, so the idea is that most people who have Non-24 have  
24 a tau or a circadian period that's longer than 24 hours,  
25 right?

CROSS-EXAMINATION - DR. CZEISLER

1 A. Yes.

2 Q. So the goal of treatment is to advance their rhythms  
3 or shorten that tau, correct?

4 A. Yes.

5 Q. Okay. And so if we look at this graph here on  
6 PDX-11.25, the portion where the curve is above the line  
7 indicates a period in which the phase is going to be  
8 advanced.

9 A. Yes.

10 Q. Right?

11 And the period where the curve is below the  
12 line, the axis is the area where the phase is going to be  
13 delayed.

14 A. Yes.

15 Q. Right.

16 And so the point that you're making is that you  
17 give tasimelteon or melatonin at time two, indicated here  
18 shortly before the habitual sleep time, you might have sort  
19 of the perverse effect of delaying rather than advancing the  
20 circadian rhythm.

21 That was why you said it was not apparent that  
22 you would give it at that time, right?

23 A. Yes.

24 Q. Right. But in patients with Non-24, the curve that  
25 we're looking at is constantly shifting, right? And so

CROSS-EXAMINATION - DR. CZEISLER

1 it's -- if you can imagine, each day it processes a little  
2 further to the right, yes?

3 A. Yes. And that was true of the people -- of the  
4 sighted people in the study. That's why it's a good model  
5 for Non-24 because they were also -- they were being studied  
6 in near darkness, and they were also drifting just like the  
7 blind people.

8 Q. Right. But then what happens, if the curve is  
9 shifting, there will come a time where a dosage administered  
10 at time two here will actually be in the advanced phase of  
11 the curve. It will be hitting the curve at a point where  
12 the curve is above the line rather than below the line,  
13 right?

14 A. Yes, I explained that in my direct testimony.

15 Q. Yes. And in that instance --

16 A. I said that if it moves over to the right, it is  
17 going to gradually move over to the right if you give it at  
18 the same time each day.

19 But what the problem is that the -- and,  
20 unfortunately, I had to take out these slides, but the  
21 circadian rhythm of sleep propensity is such that they  
22 ironically were different than most other mammals. We don't  
23 take little rat naps and cat naps throughout the day. We  
24 have this marathon of 16 hours of wakening and then a  
25 consolidated bout of sleep. And how do we achieve that?

CROSS-EXAMINATION - DR. CZEISLER

1           The circadian pacemaker, the internal clock in  
2           the brain, actually sends a stronger and stronger drive of  
3           awaking as the day progresses, peaking just before the usual  
4           time of darkness, which is when -- just before melatonin is  
5           endogenously released.

6           And it is very difficult to sleep during what we  
7           call the wake maintenance zone, in that couple of hour  
8           window before our usual bedtime, before the daily sleep  
9           episode begins. And we probably evolved that way so that we  
10          got to a safe place to sleep before it became dark and then  
11          we couldn't see anything, what's going on.

12          So there's this tremendous surge of wake and  
13          drive so that as that curve, as Attorney Rozendaal was  
14          explaining, so that curve shifts to the right so it's now  
15          being given at the time -- as that slips to the right, the  
16          reason why I said that this would give them all delayed  
17          sleep-wake phase disorder is that then the blind people  
18          would be trying to sleep at the time of maximum sleep drive  
19          emanating from the circadian clock because that would slip  
20          into that wake maintenance zone. It would slip into their  
21          desired sleep time.

22          And that's why I said I could write -- if the  
23          trial failed, I would write an entire paper explaining why  
24          it failed.

25          Q.       Doctor, do you remember the question I asked you?



CROSS-EXAMINATION - DR. CZEISLER

1 A. Yes. You asked me wouldn't it slip to the right,  
2 and I said --

3 Q. Right. And the answer to that --

4 A. I explained that --

5 Q. Pardon me, sir.

6 The answer to that question is yes, it would  
7 slip to the right and there would come a time when a dosage  
8 given at what's marked with 2 on the diagram would be in the  
9 phase advance portion and not the phase delay portion.

10 Right?

11 A. That is correct.

12 Q. Okay. Thank you.

13 Now, this effect was known in the prior art,  
14 right?

15 A. Which effect?

16 Q. The effect that the -- because of the shifting, it  
17 doesn't actually matter. One can achieve entrainment  
18 regardless of where in the cycle one administers the  
19 melatonin or the melatonin agonist.

20 A. Yes.

21 Q. In fact, there was a paper on this that Dr. Lewy and  
22 Dr. Emens published, right, in -- I think it was 2004. Does  
23 that ring a bell?

24 A. They published many papers. Can you tell me which  
25 paper?

CROSS-EXAMINATION - DR. CZEISLER

1 Q. Let's pull up DTX-155, please. Do you recognize this  
2 paper?

3 So here we have a paper, and if you focus on  
4 sort of the bottom part of the abstracts, starting where --  
5 about four lines from the bottom, the end of the four lines,  
6 it says: It does not appear?

7 A. Do I have this in my binder?

8 Q. You do. It should be DTX-155.

9 THE COURT: Mr. Rozendaal, while Dr. Czeisler is  
10 looking for that, how much more do you have?

11 MR. ROZENDAAL: I confess it's going a tad  
12 slower than I hoped it might, Your Honor. Maybe another  
13 20 minutes.

14 THE COURT: Maybe we should break for lunch.

15 MR. ROZENDAAL: All right.

16 THE COURT: I have that the plaintiffs have used  
17 their time, and then you have a little more than a half hour  
18 for your case. Okay.

19 MR. ROZENDAAL: Well, it might be a little less  
20 than 20 minutes, then, Your Honor.

21 THE COURT: So you need to figure out, you know,  
22 what had the plaintiff expected on any cross from Dr. Emens?

23 MR. GROOMBRIDGE: I think I heard -- I think  
24 it's yesterday, but --

25 THE COURT: You've already exhausted it. The

CROSS-EXAMINATION - DR. CZEISLER

1 question is, what did you expect?

2 MR. ROZENDAAL: It would be redirect for them,  
3 right?

4 MR. GROOMBRIDGE: No, cross.

5 MR. ROZENDAAL: Oh, for Dr. Emens. I apologize.

6 THE COURT: Right now they don't have any  
7 time left --

8 MR. GROOMBRIDGE: I had expected five minutes.

9 THE COURT: On redirect?

10 MR. GROOMBRIDGE: Oh, for redirect for this  
11 witness?

12 THE COURT: Yes.

13 MR. GROOMBRIDGE: At the moment I wouldn't have  
14 any.

15 THE COURT: Okay. That's good. All right.

16 So we're going to break. How long do you need  
17 for lunch?

18 MR. ROZENDAAL: A half hour seems to have been  
19 the standard.

20 THE COURT: What about the witness? Are you  
21 guys going to have sandwiches in the building?

22 MR. GROOMBRIDGE: We do, Your Honor.

23 THE COURT: Okay. So is half an hour sufficient  
24 then?

25 MR. GROOMBRIDGE: Yes.

CROSS-EXAMINATION - DR. CZEISLER

1 THE COURT: All right. We're going to come back  
2 at 2:00.

3 All right. Now, here's what we're going to do.  
4 Mr. Groombridge, you have total time left for your side of  
5 10 minutes. You can allocate it as you like. That's all  
6 you get. I have been fair.

7 And so that means, Mr. Rozendaal, you have in  
8 total time, cross this witness and present Dr. Emens, you  
9 get 35 minutes.

10 MR. ROZENDAAL: Understood, Your Honor. Thank  
11 you.

12 THE COURT: All right. We're going to break for  
13 lunch. Thank you.

14 (Recess taken.)

15 BY MR. ROZENDAAL:

16 Q. Dr. Czeisler, you testified that you participated in  
17 an FDA advisory committee meeting for Hetlioz.

18 Do you recall that?

19 A. Yes.

20 Q. And Hetlioz, the indication for which approval was  
21 being sought, was for treatment of Non-24?

22 A. Right.

23 Q. So let's take a look at the comments that you made at  
24 that advisory committee meeting.

25 MR. ROZENDAAL: And if we can go to PTX-263,

CROSS-EXAMINATION - DR. CZEISLER

1 please, at Page 30.

2 BY MR. ROZENDAAL:

3 Q. You can follow along in your binder, if you'd like.

4 And let's go down to the sixth or so comment on  
5 Page 30.

6 Are you with me, Doctor?

7 A. Yes.

8 Q. Okay. So this is a comment from Charles Czeisler.  
9 That's you, right?

10 A. Yes.

11 Q. And you said to the FDA: Melatonin has been shown to  
12 be effective in pioneering studies that were carried out by  
13 both Dr. Robert Sack and Dr. Steven Lockley who did a  
14 series -- each did a series of patients and evaluated  
15 melatonin in a sample.

16 Right?

17 So when you say melatonin is shown to be  
18 effective, you mean melatonin has been shown to be effective  
19 in entraining patients, right?

20 A. Yes. As we heard yesterday in one of the trials, it  
21 entrained three out of the seven, I believe, and in another  
22 trial it entrained something like six out of ten.

23 Q. Right. And then the last sentence of your comment  
24 you say: But certainly the use of melatonin was -- the  
25 efficacy of melatonin was inspirational to this melatonin

CROSS-EXAMINATION - DR. CZEISLER

1 agonist and to its evaluation.

2 When you say "this melatonin agonist," in that  
3 context you mean -- you mean tasimelteon, right?

4 A. Yes.

5 MR. ROZENDAAL: And I apologize. It has been  
6 brought to my attention that I may have neglected to move  
7 the admission of PTX-263.

8 BY MR. ROZENDAAL:

9 Q. Dr. Czeisler, we agree that this was a document that  
10 you considered in your work on this case?

11 A. Yes.

12 Q. You're familiar with it?

13 A. Yes.

14 MR. ROZENDAAL: We move for the admission of  
15 PTX-263.

16 MR. GROOMBRIDGE: No objection.

17 THE COURT: All right. It's admitted.

18 (PTX-263 admitted into evidence.)

19 BY MR. ROZENDAAL:

20 Q. Right. And when you said that, "the efficacy of  
21 melatonin was inspirational to tasimelteon and its  
22 evaluation," you were saying that the fact that melatonin  
23 could be successful in entraining some patients with Non-24  
24 was inspirational to developing a treatment that was safe  
25 and effective for these patients that involved tasimelteon,

CROSS-EXAMINATION - DR. CZEISLER

1 right?

2 A. That's correct. I mean, there -- as has been  
3 discussed, tasimelteon is a melatonin agonist. It binds to  
4 the MT-1 and MT-2 receptors.

5 THE COURT: Dr. Czeisler, in fairness, you know,  
6 I limited the time of people.

7 THE WITNESS: Oh, that's right.

8 THE COURT: So you answered his question.  
9 Mr. Groombridge, if he decides he wants to use that  
10 10 minutes to get his answer, he knows how to do that.

11 So thank you.

12 BY MR. ROZENDAAL:

13 Q. Even today, Dr. Czeisler, physicians use melatonin to  
14 treat Non-24; isn't that right?

15 A. Yes.

16 Q. It would not surprise you if more people took  
17 melatonin than took tasimelteon for the treatment of Non-24;  
18 is that correct?

19 A. That's correct.

20 Q. You're not aware of any head-to-head trial comparing  
21 the efficacy of tasimelteon in treating Non-24 as compared  
22 to the efficacy of melatonin in treating Non-24, are you?

23 A. I am not.

24 Q. Now, one of the effects of tasimelteon is to induce  
25 sleepiness, correct?

CROSS-EXAMINATION - DR. CZEISLER

1 A. Yes.

2 Q. And so one reason one might want to take  
3 20 milligrams of tasimelteon near bedtime is to take  
4 advantage of the soporific effect that the drug has,  
5 correct?

6 A. Yes, as Dr. Emens has described.

7 Q. All right. You're not aware of anyone apart from  
8 Vanda who tried to develop a tasimelteon product to treat  
9 Non-24 and failed, are you?

10 A. Tasimelteon?

11 Q. Yes.

12 A. No. I had recommended it to Bristol-Myers Squibb  
13 that they do such a study, but they did not.

14 Q. Okay. Now, ramelteon is also a melatonin agonist,  
15 correct?

16 A. Yes.

17 THE COURT: I'm sorry, it seems I have lost  
18 connectivity.

19 (Discussion held off the record.)

20 BY MR. ROZENDAAL:

21 Q. Ramelteon is a melatonin agonist; is that correct?

22 A. Yes.

23 Q. And it has been approved by the FDA for treatment of  
24 insomnia, right?

25 A. Yes.



CROSS-EXAMINATION - DR. CZEISLER

1 Q. There have not been any clinical trials of ramelteon  
2 in Non-24 patients, have there?

3 A. No, not that I'm aware of.

4 Q. And it'd be fair to say that there are more people in  
5 the United States to suffer from insomnia than suffer from  
6 Non-24; is that right?

7 A. Yes.

8 Q. Dr. Czeisler, you are a board-certified sleep  
9 specialist, but you are not board certified to care for  
10 patients, correct?

11 A. Correct.

12 Q. You've never been a licensed physician; is that  
13 right?

14 A. Correct.

15 Q. You do not prescribe medicine to patients?

16 A. No, I do not.

17 Q. You have not actually treated a patient for Non-24  
18 yourself?

19 A. I have not.

20 Q. All right. And let's just touch briefly on your  
21 relationship with Vanda.

22 So apart from your work in this litigation, you  
23 provide consulting services to Vanda, do you not?

24 A. That's correct.

25 Q. You've been doing so more than a decade; isn't that

CROSS-EXAMINATION - DR. CZEISLER

1 right?

2 A. Since 2004.

3 Q. And you are, in fact, the chairman of the scientific  
4 advisory board for Vanda; isn't that right?

5 A. Well, yes. I mean, it's a board of one.

6 Q. You are the scientific advisor for Vanda. Okay.

7 And for your consulting services, Vanda pays you  
8 a monthly retainer, right?

9 A. That's correct. \$8,500 a month.

10 Q. 500- -- how much a month?

11 A. \$8,500 a month.

12 Q. All right. So more than \$100,000 a year.

13 A. Correct.

14 Q. Okay. And most of your consulting work for Vanda has  
15 related to tasimelteon, right?

16 A. That's correct.

17 Q. This consulting contract you have is renewed from  
18 time to time, isn't it?

19 A. It's an automatic -- as I recollect, it's  
20 automatically renewable.

21 Q. Is it possible that the testimony you give today  
22 could have an impact on whether that contract is renewed?

23 A. I doubt it.

24 Q. All right. You also own some stock in Vanda,  
25 correct?

REDIRECT EXAMINATION - DR. CZEISLER

1 A. I do.

2 Q. The value of that stock is probably somewhere between  
3 one and a half to \$2 million?

4 A. Correct.

5 Q. Is it fair to say that if Vanda were to lose this  
6 litigation, the value of your Vanda stock could go down  
7 significantly?

8 A. The value of that stock fluctuates all the time.

9 Q. So, yeah, it could go down a lot, right?

10 A. I don't know the answer to that question.

11 MR. ROZENDAAL: No further questions, Your  
12 Honor. I pass the witness.

13 THE COURT: Any redirect?

14 REDIRECT EXAMINATION

15 BY MR. GROOMBRIDGE:

16 Q. Just really one question, Doctor.

17 Mr. Rozendaal asked -- pointed out that some  
18 people are treated with melatonin for Non-24. Of the ones  
19 who were treated with Hetlioz, in your opinion could they be  
20 effectively treated with melatonin?

21 A. Most of the people who are prescribed Hetlioz have  
22 already tried melatonin and melatonin has failed. In fact,  
23 they have suggested that people try that first before going  
24 to tasimelteon.

25 MR. GROOMBRIDGE: Thank you. No further

## DIRECT EXAMINATION - DR. EMENS

1 questions.

2 THE COURT: All right.

3 When do you understand that tasimelteon was  
4 first available for prescription?

5 THE WITNESS: In 2014.

6 THE COURT: And you started working for Vanda in  
7 2004?

8 THE WITNESS: 2004.

9 THE COURT: Okay. And why were you at the FDA  
10 meeting?

11 THE WITNESS: I was there on behalf of Vanda.

12 THE COURT: Okay. All right.

13 Thank you. You may step down.

14 THE WITNESS: Thank you.

15 (Witness excused.)

16 MR. GROOMBRIDGE: At this point, Your Honor, we  
17 rest.

18 THE COURT: All right.

19 MR. MILLIKEN: Your Honor, defendants call  
20 Dr. Jonathan Emens to the stand. And I promise this will be  
21 brief.

22 (Dr. Emens, having been previously sworn,  
23 testified as follows:)

24 THE COURT: All right. Doctor, I remind you you  
25 are under oath.

DIRECT EXAMINATION - DR. EMENS

1 MR. MILLIKEN: Your Honor, you had asked  
2 Dr. Emens a question about his CV in his first round of  
3 testimony, I just wanted to note that all the experts' CVs  
4 are appended to the pretrial order that was filed in this  
5 case.

6 THE COURT: Why have you all been introducing  
7 them into evidence?

8 MR. MILLIKEN: That's why I didn't introduce it  
9 with Dr. Emens.

10 THE COURT: But you did with other doctors.  
11 Maybe not you personally, but your side did.

12 MR. MILLIKEN: Yes. Fair enough.

13 THE COURT: I was just curious.

14 MR. STONE: Speaking for our side, we want to be  
15 certain that that counted as actually in evidence as opposed  
16 to provided to the Court in advance, out of an abundance of  
17 caution.

18 THE COURT: The only reason I asked, I thought  
19 he was the only one who didn't have a CV introduced. I was  
20 just curious.

21 One thing is you all want these bench trials.  
22 One of the negatives is, I'm curious about certain things  
23 and I get to ask questions, so it goes with the territory.

24 I much prefer jury trials, as Ms. Jacobs knows.

25 DIRECT EXAMINATION

DIRECT EXAMINATION - DR. EMENS

1 BY MR. MILLIKEN:

2 Q. All right. Dr. Emens, welcome back.

3 A. Thanks.

4 Q. Dr. Emens, were you in the courtroom just now when  
5 Dr. Czeisler testified?

6 A. I was.

7 Q. And did you hear him testify that as of January 2012  
8 in his opinion there was a long-felt need for an effective  
9 treatment for Non-24?

10 A. I did.

11 Q. And do you agree with that opinion?

12 A. With great respect, I strongly disagree with that  
13 opinion.

14 Q. And why do you disagree with that opinion?

15 A. Well, we had melatonin and we had clear data showing  
16 that melatonin could effectively entrain the circadian  
17 pacemaker and improve sleep in both instances in blind  
18 individuals with Non-24.

19 And that was really, really clear at that point.  
20 The American Academy of Sleep Medicine issued two sets of  
21 practice parameters using two separate task forces and  
22 reached the same conclusion that that was the effective  
23 treatment for Non-24. And that was what was being  
24 recommended to sleep physicians in this country.

25 Q. And Dr. Emens, do you have a sense, based on whatever

DIRECT EXAMINATION - DR. EMENS

1 data that's available that you're aware of, about what  
2 proportion of Non-24 patients entrain when they're treated  
3 with melatonin?

4 A. Yeah. So from our 2015 practice parameters, we did a  
5 meta-analysis, a very rigorous meta-analysis where we were  
6 very, very strict. And even under those strict conditions  
7 of who we included, what subjects and what studies we  
8 included in that meta-analysis, 60 percent or two-thirds of  
9 the blind patients with Non-24 entrained.

10 And I would just say as an aside, again, that's,  
11 I would say, the lowest estimate. So, for example, the Lewy  
12 and Emens 2004 paper that you saw there, we entrained  
13 100-fold percent of those individuals. And that was what I  
14 think I was talking about yesterday as part of the  
15 optimization process. By optimizing dose and optimizing  
16 time of administration, which we did in the early 2000s, we  
17 were able to successfully entrain blind individuals with  
18 Non-24.

19 And furthermore, by the early 2000s, we had  
20 figured out how to entrain them to the right time which was  
21 a topic that was discussed this morning.

22 Q. Thank you, Dr. Emens.

23 Did you hear Dr. Czeisler talk some about the  
24 FDA advisory committee meeting where there were some Non-24  
25 patients in whom melatonin had been ineffective and they

DIRECT EXAMINATION - DR. EMENS

1 testified at that meeting?

2 A. Yes.

3 Q. Have you reviewed the transcript of that meeting?

4 A. I have.

5 Q. In your review of that transcript, did you see any  
6 testimony there from any of the 67 percent of melatonin --  
7 Non-24 patients who -- in whom melatonin was effective?

8 A. I did not.

9 MR. MILLIKEN: And, Your Honor, just for  
10 housekeeping purposes, Dr. Emens's CV is DTX-397.

11 I would move that in, if there's no objection.

12 MR. GROOMBRIDGE: No objection.

13 THE COURT: All right. It's admitted.

14 (DTX-397 admitted into evidence.)

15 BY MR. MILLIKEN:

16 Q. Dr. Emens, you're a VA physician; is that right?

17 A. I am.

18 Q. How large is the VA healthcare system?

19 A. We serve about 9 million enrollees. We have 171  
20 medical centers around this country. It's hospitals and  
21 well over a thousand clinics.

22 Q. How does that compare to other sort of, you know,  
23 large-scale integrated healthcare systems in the United  
24 states?

25 A. I would say it's the largest fully integrated



CROSS-EXAMINATION - DR. EMENS

1 healthcare system in this country.

2 Q. Out of curiosity, have you ever prescribed  
3 tasimelteon to treat Non-24?

4 A. I have not.

5 Q. Why not?

6 A. I can't. It's not on formulary at the VA.

7 Q. Is there anything that's on formulary that has listed  
8 as an indication Non-24 sleep-wake disorder?

9 A. Yeah. So melatonin is listed on the VA formulary for  
10 treatment and indications for use for the treatment of  
11 Non-24 as well as delayed sleep-wake phase disorder.

12 Q. So the largest integrated healthcare system in the  
13 country has melatonin on its formulary and one of the listed  
14 indications is Non-24?

15 A. Yes.

16 MR. MILLIKEN: Pass the witness.

17 CROSS EXAMINATION

18 BY GROOMBRIDGE:

19 Q. Just to pick up there, Dr. Emens, the VA actually  
20 commissions the manufacturer of its own melatonin for  
21 administration to patients, correct?

22 A. Well, I believe, and, again, I am not the one  
23 commissioning the manufacturer. I believe what they  
24 actually do is they rely on a two-process model of  
25 certification of whoever manufacturers it. And I don't know

1 if they manufacture it internally.

2 Q. Fair point.

3 But what you have on formulary is something  
4 that's not available to everyone, to physicians throughout  
5 the country, correct?

6 A. Oh, I -- again, I don't think so. I think they use  
7 Rugby brand melatonin, which, again, is certified by FDA  
8 under the FDA's good manufacturing practice as having the  
9 right dosage and not having any impurities.

10 So I don't think you have to go to a VA to get  
11 Rugby brand melatonin. I think you can get it online  
12 actually.

13 MR. GROOMBRIDGE: Thank you. No further  
14 questions.

15 THE COURT: All right. You may step down, thank  
16 you.

17 MR. MILLIKEN: No redirect, Your Honor.

18 THE COURT: All right. So you all rest.

19 MR. ROZENDAAL: That concludes our case, Your  
20 Honor.

21 THE COURT: Thank you.

22 MR. ROZENDAAL: And I suppose for good  
23 housekeeping, we ought to renew our 52(c) motion for partial  
24 judgment on judgment for partial findings for  
25 noninfringement.

1 THE COURT: Right. Can I just -- let's just  
2 deal with one thing housekeeping, since we just touched on  
3 long-felt, so there's a blocking patent, right?

4 MR. GROOMBRIDGE: There --

5 THE COURT: There's a compound patent.

6 MR. GROOMBRIDGE: There's a compound patent.

7 THE COURT: Right. Presumably for treatment for  
8 Non-24?

9 MR. GROOMBRIDGE: Would cover the use of  
10 tasimelteon for anything.

11 THE COURT: Right.

12 Is there just a claim which says nothing more  
13 than a method to treat or just says the treatment of  
14 patients with Non-24 disorder with tasimelteon?

15 MR. GROOMBRIDGE: In the blocking patent?

16 THE COURT: In any patent.

17 MR. GROOMBRIDGE: Well, there's the claims that  
18 are in litigation here.

19 THE COURT: Well, does any one of those claims  
20 limit it to that?

21 MR. GROOMBRIDGE: To tasimelteon?

22 THE COURT: No, no. Is there any claim that all  
23 it says is the use of tasimelteon to treat people with  
24 Non-24 disorder?

25 MR. GROOMBRIDGE: There's no claim that says

1 just that.

2 THE COURT: Right. So there's a nexus  
3 requirement long-felt needs.

4 MR. GROOMBRIDGE: Yes.

5 THE COURT: The testimony you elicited was there  
6 a long-felt need for the treatment of people with Non-24  
7 disorder. And you got an answer that was yes.

8 Without even assessing the credibility of that  
9 testimony, isn't that the end of the matter? That we don't  
10 have any -- you got to demonstrate some nexus to the  
11 limitations that are at issue in this case. And so, I'm  
12 just wondering for, in terms of, like, trying to be  
13 efficient, if that issue is out of the case.

14 MR. GROOMBRIDGE: I don't think so, Your Honor,  
15 because I think the nexus can be shown. There's only one  
16 approved indication here. And, so, the only thing that  
17 tasimelteon can sold for is the treatment of Non-24.

18 THE COURT: But you have to -- there's no -- I  
19 just asked you: Is there any claim limited to just the  
20 treatment of Non-24 with tasimelteon? And you said no.

21 And I think you're right, that every other claim  
22 that you've asserted -- and my guess is for validity  
23 reasons -- has some other limitation, including the  
24 entrainment reissued patent, right. Even if I held it was  
25 limiting, I believe at your request, probably to make sure

1 that patent claim was not invalidated, I'm going to guess,  
2 but -- because it's not often that I have a plaintiff who  
3 wants to limit a claim, but you did.

4 So my question is, you know -- and, again, I'm  
5 really trying to limit what I have to decide when -- and it  
6 just seems to me, as I listen to all of this, there's no  
7 nexus at all to any long-felt need evidence to a limitation  
8 that's at issue in our case.

9 MR. GROOMBRIDGE: I guess the way we would see  
10 it, Your Honor, is that the only thing that was out there  
11 was melatonin, and that doesn't work for people.

12 And that the nexus case may rise or fall with  
13 the infringement case. But in our view, the -- you can't  
14 treat Non-24 with tasimelteon without being covered by at  
15 least one of these patents; specifically the reissued  
16 patent. And probably -- not to say I haven't thought the  
17 issue through, but I suspect the others.

18 THE COURT: All right. So that's your only  
19 argument. That would be the only claim that you have  
20 adduced evidence for, in your opinion, is long-felt need is  
21 the entrainment claim?

22 MR. GROOMBRIDGE: I'd have to think that  
23 through, but standing here right now I don't think of any  
24 others.

25 THE COURT: Okay.

1 All right. Well, I thought -- well, we'll  
2 just -- that will be one more issue I guess we'll have to  
3 brief and listen to.

4 Okay. Anyway so you're first. Go ahead.

5 MR. GROOMBRIDGE: So, Your Honor, we did put  
6 together some slides that's useful.

7 THE COURT: What are we doing right now?

8 MR. GROOMBRIDGE: I thought we were doing the  
9 Markman presentation.

10 THE COURT: I thought people wanted to get their  
11 motions for housekeeping stated. I thought that's why you  
12 stepped up.

13 MR. GROOMBRIDGE: Oh, I'm sorry, we oppose the  
14 renewed motion.

15 THE COURT: I thought you were going to make  
16 one. Okay.

17 MR. GROOMBRIDGE: Frankly, we saw little reason  
18 to do that, given the procedural posture of the case.

19 THE COURT: Well, okay. I'll let you do -- you  
20 guys know enough about preserving your right on appeal and  
21 all sorts of things, so I'll leave it to you.

22 Mr. Rozendaal?

23 MR. ROZENDAAL: I will go ahead, Your Honor, and  
24 ask for judgment as a matter of law in our favor on the  
25 invalidity limitations. I think that --

1 THE COURT: How about this, I'm going to reserve  
2 ruling on it.

3 All right. Any other motions?

4 MR. GROOMBRIDGE: Ms. Jacobs is more -- is  
5 closer to this issue than me and probably wiser.

6 MS. JACOBS: Your Honor, our understanding that  
7 unlike in a jury trial that 52, Rule 52 motion is  
8 discretionary as opposed to waiver, but --

9 THE COURT: And that's great. Like I said, I'm  
10 leaving it up to you all.

11 MS. JACOBS: But for purposes of just the  
12 record, we will make the motion, both infringement and  
13 invalidity and reserve based -- and we'll brief it at the  
14 appropriate time.

15 THE COURT: Sounds good to me. That sounds  
16 great to me.

17 MS. JACOBS: Thank you, Your Honor.

18 THE COURT: All right. So then let's do the  
19 Markman hearing and then there is -- how many terms,  
20 Mr. Groombridge, do I need to construe?

21 MR. GROOMBRIDGE: My understanding was the only  
22 thing we're talking about is the Claim 10 of the '465 patent  
23 and the -- well, really the term is in Claim 1, since Claim  
24 10 depends on it. The meaning of the term "with a reducing  
25 agent and an acid." And that was the issue that had come

1 up.

2 THE COURT: What's the patent for the period of  
3 sleep?

4 MR. GROOMBRIDGE: It's the reissued --

5 THE COURT: It's also the reissued?

6 MR. GROOMBRIDGE: Yes.

7 THE COURT: The contact and reacting is the '465  
8 patent, that's what we're going to talk about?

9 MR. GROOMBRIDGE: Yes.

10 THE COURT: And there was also -- there was  
11 some -- where's the period of sleep you said in that patent?

12 MR. GROOMBRIDGE: It's in the reissued '604, but  
13 Your Honor, we were not aware there was any claim  
14 construction issue with respect to that.

15 MR. ROZENDAAL: Your Honor, I think there's a  
16 dispute over what the plain and ordinary meaning of daily  
17 sleep period is.

18 THE COURT: Well, see that's what occurred to me  
19 listening to the evidence come in and that's why I thought  
20 we might -- well, I guess, I mean, what do I sua sponte do  
21 my construction of the claim -- during briefing, I feel like  
22 I've got to do it, is that right?

23 MR. GROOMBRIDGE: Yes, Your Honor, you can.

24 THE COURT: Okay.

25 MR. GROOMBRIDGE: And if Your Honor is hearing



1 closing argument, we'd be happy to address that as well.

2 THE COURT: What do you think the daily sleep  
3 period is?

4 MR. GROOMBRIDGE: We think when a person wants  
5 to be asleep, but is not necessarily sleeping for that  
6 entire period.

7 THE COURT: And you think it means the person is  
8 mostly asleep during 7 to 9 hours.

9 MR. ROZENDAAL: Correct. Because it's a sleep  
10 period and not a sleep opportunity period, as Dr. Emens  
11 explained.

12 THE COURT: All right. Well, let's deal --  
13 let's talk about the one that you both agree we do need to  
14 construe, which is the '465 patent.

15 MS. JACOBS: May we approach with slides, Your  
16 Honor?

17 THE COURT: Yes. Sure. Please.

18 MR. GROOMBRIDGE: Thank you. I'll get started  
19 whenever Your Honor is ready.

20 THE COURT: I'm sorry. Go ahead, thank you.

21 MR. GROOMBRIDGE: So, Your Honor, I think the  
22 parties are in agreement that this is part of a so-called  
23 product-by-process limitation to which Mr. Rozendaal alluded  
24 earlier in the trial, which is a particular form of claim.  
25 And the Federal Circuit has said essentially came into being

1 to enable patent applicants to claim that something where  
2 there might be difficulty in knowing exactly what it was,  
3 for example, chemically so they could recite the process by  
4 which it is made. And I think we all agree on that.

5 We think that that is significant because of the  
6 context of the product-by-process claim. It's a type of  
7 claim that would direct the reader or the interpreter back  
8 to the specification more, perhaps, than other types of  
9 claims; specifically informed by how the material is made.  
10 And the -- and I think what the dispute boils down to -- I  
11 know -- it turns on the meaning of the word "and."

12 And we submitted this to the Court yesterday --

13 THE COURT: Which "and?"

14 MR. GROOMBRIDGE: This "and."

15 I'm sorry. "And an acid," so it's --

16 THE COURT: I'm not so sure you're right. I  
17 mean the first "and" I think is actually part of the issue;  
18 "and contact."

19 MR. GROOMBRIDGE: Well, I guess what we would  
20 say -- first of all, I think, Your Honor, that we don't  
21 disagree with the testimony that contacting and reacting --  
22 it seems to be common ground that in order to react you have  
23 to have contact. And we passed through the patent trying to  
24 find, you know, was there anything that gave some special  
25 meaning to contacting or informed this and, frankly, we

1       didn't find it.

2               THE COURT:   Right.   But as I pointed out, I  
3       think it's example six, actually has the words "contacting  
4       and reacting" and then it's got a sentence that follows it  
5       that limits it to reacting.   So you would think that  
6       contacting must have some meaning, it just can't be  
7       superfluous.

8               MR. GROOMBRIDGE:   Our reading of it was that it  
9       may be -- it's not clear that it does have meaning other --  
10      I mean since there can't be a reaction without contact.

11              THE COURT:   But, see, no -- the reason why it  
12      could have meaning here is because if you have a sequential  
13      reaction, right, you start with A and then you react it with  
14      B, A no longer exists, right, in pure form.   A has been  
15      reacted, it might be A plus, A minus, but it's A modified;  
16      you agreed with that?

17              MR. GROOMBRIDGE:   I do agree with that.

18              THE COURT:   Okay.   So then at that point you  
19      don't have A, so if you've got reacting A with B and C and  
20      you first react A with B, when you start to react it with C,  
21      A is something different.   Right?

22              MR. GROOMBRIDGE:   That's the case, Your Honor,  
23      and that's where we think product-by-process law comes into  
24      play.

25              THE COURT:   Hear me out.

1 But I can kind of understand the way that  
2 reacting is used when you have the objects joined by a  
3 conjunction, that it could be sequential, it could be  
4 simultaneous. But that's why I think contacting is  
5 different, because we don't use contacting that way. And  
6 precisely, because we say, as one of your witnesses did, it  
7 was touching. That if you contact A with B, it doesn't  
8 follow, like with reacting, that you can contact A with C if  
9 it's been modified. A no longer exists.

10 So, in other words, contacting and reacting are  
11 used differently in our language. And now they've got  
12 testimony, which I'm just putting aside for argument's sake  
13 that I don't want to decide or, you know, whether reacting  
14 has to be sequential or simultaneous, but contacting seems  
15 to be a real problem because I don't know if -- I can't  
16 conceive of something contacting two different things if  
17 it's first changed into something else.

18 MR. GROOMBRIDGE: Right. And that's why in our  
19 view contacting and reacting here means simply putting the  
20 things -- introducing them into the pot, if you will.

21 And the intent of this claim is a  
22 product-by-process claim. You start off, you put two things  
23 in the pot and then you put something else, right. That  
24 would be in some ways a classic product-by-process claim.

25 And at the end it says to prepare a defined

1 thing. And so, this is kind of right down in the middle of  
2 the fairway for a product-by-process claim. I start with  
3 something, I perform some steps and I end up with something  
4 else, right. And this is exactly why product-by-process law  
5 evolved because it is very --

6 THE COURT: Well, your client wrote the patent.  
7 Why is contacting in there? And only in there in this  
8 particular limitation and only there in some discussions of  
9 reactions in the written description, but not others. And  
10 in particular, in example six, there's some beginning steps  
11 that refer to contacting and reacting and then there's  
12 subsequent steps that it's only reacting so why did they  
13 write the patent that way?

14 MR. GROOMBRIDGE: We tried to find that out and  
15 could not get an answer, because I suspected Your Honor was  
16 going to ask me that.

17 And as I passed through the patent what I could  
18 find is it seems like they almost always said contacting and  
19 reacting, but there's places where Your Honor has pointed  
20 out where they are just saying reacting; whether or not that  
21 has significance or not, I cannot say.

22 But the -- but here what we -- you know to us  
23 the intent of this patent and this limitation is that you're  
24 performing a manufacturing step; that is, you know, as we  
25 saw in the evidence, it's often written out with a -- you

1 start with one thing and then there's an arrow and some  
2 conditions and you end up with something else.

3 And the way product-by-process law is instead of  
4 putting parenthesis around that and saying this is a series  
5 of steps where you begin with X and end with Y, right. And  
6 that's what product-by-process law is for.

7 And the fair reading of this under, you know,  
8 under that body of law is that it -- that's what's going on,  
9 you're putting some things into the pot, chemical reactions  
10 begin, you add some more things and then at the end you get  
11 a defined product out of it.

12 THE COURT: Do you have any examples in the case  
13 law where -- I mean, I got to believe reacting is commonly  
14 construed. And where our court said if it's reacting A with  
15 B and C what does it mean?

16 MR. GROOMBRIDGE: I do not. And the -- this is  
17 not reacting, but the structural formula.

18 In the Ortho-McNeil case was the one that we  
19 thought was closest, but that may get into the meaning.  
20 That's about -- it's not about reaction specifically, it's  
21 about the -- what variables on the molecule could be, right,  
22 and how you get to them. So I don't think -- I know -- I  
23 cannot stand here and say that we did a Westlaw search for  
24 patent with "reacting."

25 THE COURT: Go ahead. I interrupted your flow;

1 go ahead.

2 MR. GROOMBRIDGE: What we see -- you know  
3 applying the product-by-process teaching, what we see is you  
4 start with something and then there's an order of  
5 operations, and then you end with something else. And  
6 that's how the claims would be understood. And that -- or  
7 there would be another way of -- it's the same thought  
8 written out in slightly more scientific notation looking for  
9 the record at slide five. And the -- and this is consistent  
10 with the other claims in the patent that we got claims, for  
11 example, here where it specified that the reducing agent is  
12 -- what I at least refer to as -- lithium aluminum hydride,  
13 and that the acid is hydrochloric acid. And then in Claim  
14 14, it is both of them. And we know, and I believe this is  
15 undisputed, that -- this is how it's -- this lines up pretty  
16 much directly, this kind of a one-to-one match with what's  
17 in the specification. Looking at the figure on slide seven  
18 we've got that classic notation, if I have my beginning  
19 compound and I have the arrow with notations regarding the  
20 steps to get me to the end compound, and the claim  
21 limitation is intended to map to this, right.

22 And so, I reduce something -- this is just of  
23 course an example, but it is an example that some of the  
24 deep end of the claims are specific to. I use lithium  
25 aluminum hydride in blue as the reducing agent and then

1 after that I add hydrochloric acid -- and I'm omitting the  
2 solvents -- and then I end up with the thing that the claim  
3 specifies -- this claim element specifies as the end point.

4 And so, the claim is, in our view, directly  
5 mapping back to this reaction speed in the patent.

6 And I'll move on when Your Honor is ready.

7 And so, in the written description, which  
8 immediately follows the reaction scheme, it is written in  
9 words, describes these, talks about the lithium --

10 THE COURT: This is five we're talking about  
11 still?

12 MR. GROOMBRIDGE: I'm sorry?

13 THE COURT: We're talking about five?

14 MR. GROOMBRIDGE: Yes. So we add, first of all,  
15 the lithium aluminum hydride, the LAH, the reducing agent.  
16 And then there's a fairly lengthy description of other  
17 manipulations that are going on, not necessarily reactions.  
18 But after this there are a number of other process  
19 operations. And then -- so this is in column 14 at lines 3  
20 through 12, we run on through the end of column 14.

21 And then at the top of column 15 we come to a  
22 place where the acid is at, in this case in the form of  
23 hydrogen chloride gas. And then at the end we get out to  
24 medium five.

25 So, again, in our view, Your Honor, the claim is



1 mapping directly back to this part of the written  
2 description.

3 And when we go back and we look at the  
4 architecture of the claims, that Claims 2, 3 and 14 make  
5 that clear that the -- it must be this. In Claim 2 wherein  
6 the reducing agent is lithium aluminum hydride; Claim 3  
7 wherein the acid comprises HCL; and then Claim 14 both of  
8 those sub limitations combined.

9 So, in our view, right, there's a concordance,  
10 if you will, between the written description and the claim.

11 THE COURT: And the bottom line is scheme five  
12 is Claim 14?

13 MR. GROOMBRIDGE: Scheme five is the  
14 limitation -- yes, exactly. The limitation we're talking  
15 about.

16 And turning to the knowledge of the skilled  
17 person -- and, again, this I'm sure is common ground -- you  
18 wouldn't react lithium aluminum hydride with an acid and you  
19 wouldn't -- and you certainly wouldn't react one of these  
20 hydride reducing agents with hydrogen chloride, it won't  
21 work and it would risk an explosion. And if --

22 THE COURT: But he also says I should read the  
23 patent the way the defendants want me to read it.

24 MR. GROOMBRIDGE: Well, I mean, I'm --

25 THE COURT: That he says -- right? I mean, if I

1 look at it, it's got to be sequential -- I mean it can't be  
2 sequential.

3 MR. GROOMBRIDGE: To the extent he's talking  
4 about claim construction, I'm not sure that that's --

5 THE COURT: Well, he allowed that there are  
6 embodiments out there that would be covered by Claim 1.

7 MR. GROOMBRIDGE: I think it was, because the  
8 testimony, Your Honor, was you could do this -- you couldn't  
9 do it with a hydride reducing agent, which is specified, for  
10 example, in Claim 2 and Claim 14. You couldn't do it with a  
11 strong nonoxidizing acid, like hydrogen chloride. You might  
12 be able to do it with a weak -- with some other kind of  
13 reducing agent and a weak acid, but if that be so, then it  
14 means that Claims 2, 3 and 14 are inoperable, right. That  
15 based on this testimony, they simply never could be carried  
16 out, it just won't work.

17 Whereas if you construe it to mean reaction  
18 scheme five and you can't put in any portion of the written  
19 description in light of that, you say it's sequential, then,  
20 yes, it's all fine and it maps directly to it and we have no  
21 claim construction issue.

22 THE COURT: All right. But there are cases, the  
23 famous cookie case, where you don't claim it, right? You  
24 didn't claim an invention.

25 MR. GROOMBRIDGE: There are, right. But this to

1 us turns then down what does the word "and" mean here? Does  
2 it mean -- we say if you construe that to mean "and then"  
3 then that's fine, you know we -- sequential addition is then  
4 covered.

5 And so -- and it's clear that there are places  
6 in the written description where "and" is used to mean "and  
7 then," and we put a couple into these slides, but --

8 THE COURT: Well, make sure you go through  
9 everything because -- and, first of all, do I have to resort  
10 to extrinsic evidence to construe this claim?

11 MR. GROOMBRIDGE: I don't think one has to  
12 resort to -- I mean, I think we have testimony about the  
13 knowledge of skill in the art; we ought to bring that in. I  
14 don't know that that is extrinsic evidence.

15 THE COURT: Well, okay, but is there a dispute  
16 over who's the POSITA for this?

17 MR. GROOMBRIDGE: There's not dispute about  
18 who's the POSITA, but this is about what the POSITA would  
19 know.

20 THE COURT: Right, but I've got competing  
21 testimony on that.

22 MR. GROOMBRIDGE: I don't think there is  
23 competing expert testimony.

24 THE COURT: How to construe this claim and on  
25 whether the limitation question is sequential or

1 simultaneous, you don't think there's disputed expert  
2 testimony?

3 MR. GROOMBRIDGE: I don't think -- I'm not --  
4 Your Honor, I'm not talking about taking an expert and  
5 saying how would you understand these words. I was talking  
6 more about --

7 THE COURT: But that's actually relevant.

8 I mean, once we go to extrinsic evidence that  
9 becomes relevant. And if I've got an expert who says no,  
10 reacting A with B and C means you do it simultaneously, I  
11 mean that seems to me I could rely on that evidence, if I  
12 get to extrinsic evidence.

13 MR. GROOMBRIDGE: I could stand here and say  
14 Your Honor is foreclosed from relying on such evidence,  
15 right --

16 THE COURT: Okay. I think we have competing  
17 evidence, because I think that's what Perni says.

18 MR. GROOMBRIDGE: I have to confess I don't have  
19 top of mind what he said --

20 THE COURT: I think I pretty much asked him,  
21 because I think I pretty much said to him well, you know,  
22 maybe reacting could be sequential. And he said oh, I can't  
23 read it that way. That's my recollection of the testimony.

24 MR. GROOMBRIDGE: It may be because I am -- my  
25 sleep has not been well-aligned to my daily sleep period,

1 but I'm not recalling.

2 And I'm by no meaning saying he didn't say that

3 --

4 THE COURT: I think your bigger problem is  
5 contacting. I just think that's your biggest problem. And  
6 I haven't heard anything. I mean, you don't really have an  
7 answer for that. I'm not faulting you as an advocate, but  
8 what's the answer?

9 MR. GROOMBRIDGE: I think to us the answer is  
10 that this is a -- that contacting and reacting, if you will,  
11 is modifying not one, but several things that come after it  
12 and essentially --

13 THE COURT: You want me to read contacting out  
14 of the patent?

15 MR. GROOMBRIDGE: No.

16 MR. STONE: Your Honor, please forgive me, we  
17 have all been trying to do all this at once.

18 THE COURT: Go ahead. Confer.

19 MR. STONE: Forgive me.

20 Thank you. In the same way the constitution  
21 refers to all laws necessary and proper, and we all know  
22 that that is one phrase that means one thing at this point.  
23 Contacting and reacting are used as synonyms throughout the  
24 patent. There's a place where it says contacting this with  
25 that, but doesn't use the verb reacting. It's clearly

1 describing a reaction, there's no reason to otherwise  
2 contact them.

3 It is absolutely not consistent throughout. I  
4 do not dispute that, Your Honor. But they are used as  
5 synonyms for each other. Each of the two steps begins with  
6 the words "contacting," which I think invokes put things in  
7 a bucket and then describes how do they react with each  
8 other. But there's nothing in the patent that says that  
9 where it says contacting and reacting A with B and C, that  
10 that means that the A has to contact the C in an unchanged  
11 form, particularly where that would lead two dependant  
12 claims that embody the only example to be nonworking  
13 embodiments.

14 I take the point that the word "contacting" is  
15 sitting there saying do something with me. And it may very  
16 well be -- it will have exactly the same meaning if it just  
17 said "reacting." But throughout the patent, those words are  
18 used as synonyms; sometimes together and sometimes  
19 separately.

20 MR. GROOMBRIDGE: He said it better than I can.

21 MR. STONE: I slept half an hour more.

22 THE COURT: You both work together, you work  
23 together well, I'm happy to have that done collectively.

24 All right. So the bottom line you can't point  
25 me to anything in the patent that defines "contact,"

1 correct?

2 MR. GROOMBRIDGE: I cannot.

3 THE COURT: Okay. And you agree that reacting  
4 is used without contacting in the written description,  
5 correct?

6 MR. GROOMBRIDGE: In at least one place, yes.

7 THE COURT: I think -- okay. Well, I think --  
8 okay. You're right, it's used in at least one place and  
9 "reaction" is used multiple times with "contact."

10 MR. GROOMBRIDGE: "Reaction" certainly is.

11 THE COURT: But reacting is only used once and  
12 it's in example six?

13 MR. GROOMBRIDGE: Yes. And, for example, in --  
14 I mean, the other places that we found this is it seems like  
15 Column 7, Line 35 is an example, or Column 8.

16 THE COURT: I think there's numerous examples of  
17 contacting and reacting being used together for the phrase  
18 "contacting and reacting."

19 MR. GROOMBRIDGE: Right. And having passed the  
20 text quite a lot as one would -- as you imagine, right,  
21 it -- it seemed to us that there was no -- it didn't seem as  
22 though there's an -- intended to be a meaningful difference  
23 in the written description here, right. It's not as if they  
24 said at the beginning when I say "contacting," I mean this;  
25 or when I say "reacting," I mean that. You know, Your

1 Honor, it seems as though they're using the phrase  
2 "contacting and reacting" to mean put the things in a bucket  
3 and react them. And there's one instance where they failed  
4 to do that, they left out "contacting."

5 THE COURT: All right. And your position is I  
6 should not resort to extrinsic evidence. And, really, your  
7 argument is that if I read the limitation to require  
8 simultaneous contacting and reacting with the -- the  
9 reducing agent and the acid, I read out the embodiment --

10 MR. GROOMBRIDGE: That's correct, Your Honor.  
11 And it's -- again, where they -- to us it's sort of  
12 different; in that, where they have a defined start point  
13 and a defined end point and then they go -- for example,  
14 scheme five. And then they go to -- they take the end point  
15 the molecule that comes out of scheme five and it becomes  
16 the input to scheme six, they spell that out. They don't  
17 say "contacting and reacting" and "contacting and" -- but so  
18 each of the contacting and reacting limitations is kind of  
19 like one of those --

20 THE COURT: Except for example six.

21 MR. GROOMBRIDGE: I think so, Your Honor. And  
22 it would be our view that, you know, example six -- it could  
23 equally be explained by the fact that they simply, by error,  
24 forget -- they intended to put "contacting" --

25 THE COURT: I think that has to be your



1 position. That's the only way you can explain example six  
2 is that some scrivener forgot to put "contacting and."

3 MR. GROOMBRIDGE: Yes. Again, Your Honor, I  
4 think that --

5 THE COURT: Or he was like he bought into this  
6 necessary and proper argument that Mr. Stone is saying.

7 MR. GROOMBRIDGE: Proper, yes.

8 THE COURT: Yes.

9 MR. GROOMBRIDGE: And so that's our view.

10 And, you know, we think this is much more in  
11 line with the Ortho-McNeil, that it is in line with the  
12 cookie dough case where the question there was does "and" --  
13 is it conjunctive or disjunctive, basically does it mean --

14 THE COURT: That's a different issue.

15 MR. GROOMBRIDGE: Fair enough. But it does  
16 say -- it distinguishes the cookie dough case, Chef America,  
17 on the basis that the -- I think we might have -- that's it.

18 In Chef America you've got a situation where  
19 there's really -- there's no possible ambiguity. Whereas  
20 here, when you look at this, particularly in line with  
21 they're trying to capture what's going on in that portion of  
22 the written description, then, in our view, the certain  
23 years -- the debate to be had, at least, about what they  
24 meant. And, therefore, we wouldn't reach the Chef America  
25 principle, we'd go back and look and say how can we give

1 this meaning that accords with the written description.

2 THE COURT: What if I just find myself at  
3 equipoise. I see both sides, right.

4 What do I do in that situation?

5 MR. GROOMBRIDGE: I mean, our view of the world,  
6 Your Honor, is that this is a claim construction issue.

7 THE COURT: No, I agree. But what if in claim  
8 construction -- and I hear you read out the embodiment, I  
9 hear them say you got to give meaning put it to claim term,  
10 "contact," can't be meaningless.

11 You say not to resort to extrinsic evidence, but  
12 even if I did, I've got competing expert testimony and I  
13 have an expert who agrees with you that -- you're reading  
14 out a preferred embodiment, but at the same time says you  
15 can absolutely have this claim still cover processes, right.

16 And I'm thinking, I really can't -- this is  
17 very, very tough. Can I weigh policy consideration? Can I  
18 consider you already got a patent and now you're trying to,  
19 essentially, broaden what you got as an initial patent to  
20 keep people out of the field; can I let any of that factor  
21 into my analysis?

22 MR. GROOMBRIDGE: I don't believe so.

23 THE COURT: What should you do if you're the  
24 Court and you're really stuck?

25 MR. GROOMBRIDGE: I think unfortunately, Your

1 Honor --

2 THE COURT: This is why we get paid the big  
3 bucks.

4 MR. GROOMBRIDGE: Exactly, Your Honor.

5 Mr. Stone may have a better answer than I.

6 MR. STONE: I don't know that I do, Your Honor.

7 But, forgive me, the way I read the case law is you start  
8 with the language of the claim and then we -- as Your Honor  
9 is quite familiar -- and by the way that has to mean all the  
10 claims, it has to have Claim 2 and Claim 3, you have to have  
11 life too, it's not just the word "and," you have to look at  
12 the language of the claim. Where it is susceptible of more  
13 than one meaning --

14 THE COURT: Wait.

15 MR. STONE: Sure.

16 THE COURT: Yeah, I -- I think what you just  
17 said is a little more nuanced.

18 MR. STONE: Okay.

19 THE COURT: I think because there have got to be  
20 constructions of claims that have been upheld even when they  
21 nullified another claim in the patent.

22 MR. STONE: Absolutely.

23 THE COURT: Yeah. So that's -- what you read as  
24 a whole -- in other words, there's still a debate between  
25 I've got to give meaning to "contact" and I've got to give

1 meaning to Claim 14.

2 MR. STONE: And I did not mean to suggest  
3 otherwise, Your Honor, you are right. But when you look at  
4 what does the word "and" or what does the word "contact" or  
5 what does the word phrase mean in Claim 1; one part of  
6 considering that is what --

7 THE COURT: I agree with that.

8 MR. STONE: That's all I meant to say, it's not  
9 dispositive. But Your Honor has asked if all of this is  
10 equipoise, because they've got arguments and we've got  
11 arguments.

12 Ultimately, the fallback then becomes not  
13 leaving dependent claims inoperable. That actually is --  
14 reoccurs not only in what do the words mean question, but  
15 would this construction read out a claim. And I think that  
16 here it is agreed that Claim 2 doesn't work -- if the  
17 ingredients are edited simultaneously because, as we heard  
18 from both experts, it would explode.

19 And so, ultimately I think the law provides --  
20 you can then get further down to construing claims to  
21 preserve invalidity, which is not an issue here. But the  
22 patent can be read, the claim can be read in a way -- or at  
23 least one can get to the analysis -- what does this do for  
24 Claim 2, what does this do for --

25 THE COURT: So you are saying that giving

1 meaning to a claim is more important than giving meaning to  
2 a word in --

3 MR. STONE: Oh, I am not, Your Honor.

4 THE COURT: Well, I think that is what you're  
5 saying.

6 MR. STONE: No, I'm saying --

7 THE COURT: The way I look at it is to preserve  
8 Claim 13, 2 and 3, I have to conclude that "contact" doesn't  
9 mean anything. If I reach that conclusion, which I read --

10 MR. STONE: I misunderstood you, Your Honor.

11 I thought you meant if you are at equipoise  
12 about what to do with contacting, what then do we do to  
13 break the --

14 THE COURT: No, I'm talking about I'm at  
15 equipoise about the whole construction of the limitation.  
16 And I've concluded that I can't give meaning to "contact"  
17 unless I read this as requiring simultaneous mixing as  
18 oppose to sequential mixing. And I can't give meaning to  
19 contact if I do that.

20 On the other hand, I realize if I give meaning  
21 to contact, I'm reading Claim 14 out of the patent.

22 Okay. That's what I'm saying, what do you do.  
23 Is there a -- at that point, is there something that comes  
24 in and says here's the dispositive question?

25 MR. GROOMBRIDGE: I don't think there is a tie

1 breaker, in the sense of like in terms of policy or I can  
2 use discretion or those things. I think for better or  
3 worse, it's like a statue, I have got to answer the question  
4 and one way or the other; it just has to be an answer.

5 THE COURT: All right. Thank you.

6 MR. GROOMBRIDGE: Unless Your Honor has further  
7 questions --

8 THE COURT: I might, but let's hear from  
9 Mr. Rozendaal.

10 MR. GROOMBRIDGE: Okay.

11 MR. ROZENDAAL: Mr. Brooks, can you go ahead and  
12 pull up JTX-6, I think. Just do Claim 1 would be fine.  
13 Here we go.

14 So, Your Honor, I don't have any slides, you  
15 know we are on the generic side.

16 THE COURT: That's fine.

17 MR. ROZENDAAL: I guess I would start by saying  
18 that I don't think this is a problem with "and," and I don't  
19 think that the proposed solution that Vanda has put forward  
20 by just sticking the word "then" in -- in their letter to  
21 Your Honor they said you can basically -- we think the plain  
22 meaning is "and then contacting" with or -- yes, with an  
23 acid.

24 I don't think that solves the problem, because  
25 you need to contact and react the carboxamide with a

1 reducing agent. And everybody agrees that the reducing  
2 agent has to both touch and have a reacting chemical  
3 interaction with the carboxamide.

4 THE COURT: I don't think they agree with that.

5 MR. ROZENDAAL: I think they do.

6 THE COURT: Well, I don't because -- well,  
7 because they admit that the carboxamide is modified once it  
8 touches the reducing agent.

9 MR. ROZENDAAL: Right. But at least the  
10 reducing agent has to touch the carboxamide, even in their  
11 view of the world.

12 THE COURT: Right.

13 MR. ROZENDAAL: And it has to react. The  
14 reducing agent and the carboxamide has to react.

15 THE COURT: Correct.

16 MR. ROZENDAAL: All right. So far so good.

17 And then even if you stick the word "then" in,  
18 it says "and then an acid."

19 THE COURT: Yeah, well, that's why I agreed to  
20 it if you say it can't be modified.

21 MR. ROZENDAAL: Right. Because it's still the  
22 case that the thing that needs to be reacted with the acid  
23 or contacted with the acid is the carboxamide.

24 THE COURT: I agree.

25 MR. ROZENDAAL: What they would need to do to

1 get what they want is they would need to do a contacting and  
2 reacting the carboxamide with a reducing agent and -- and  
3 then contacting and reacting the product of that reaction  
4 with an acid to form -- you know, and it would look like  
5 that.

6 And so, I don't think that it's just a question  
7 of well, let's look at the dictionary for "and" and pick a  
8 definition we like. I think they have a structural problem  
9 with the way the claim is written. And it's illustrated by  
10 the fact there are two contacting and reacting steps, right.

11 So you do a reaction that produces the  
12 methanamine in the first step and then when they want you to  
13 do something to that intermediate product, they put in a  
14 whole separate step. So I think the structure -- the way  
15 the claim is written indicates to one when you have an  
16 intermediate product and when you don't. And so, that's  
17 why, we think, just as a matter of grammar and structure,  
18 the plain meaning of this claim is really not ambiguous and  
19 they're stuck with it.

20 And in further support of that, I would point  
21 Your Honor to the case that we cited in our letter submitted  
22 March 30th, *TFH versus Hearts Mountain*, that's 67 Federal  
23 Appendix 599 at 602 to 603. I know federal appendix is an  
24 unpublished case, but I think Your Honor will find the  
25 language -- it's strikingly close to our facts, right.



1           There the Court said: "The unambiguous meaning  
2 of the words 'the reaction of A and B' precludes any  
3 construction that might embrace the presence of an  
4 intermediate compound or intervening step."

5           So the claim said "the reaction of A and B" and  
6 the proposed construction was -- it was well, that means you  
7 react A with something and then you react B with something.  
8 And the Federal Circuit said no, no, no, no. Reacting A and  
9 B means that those two things have to react, you can't react  
10 A with something to make something else and then react that  
11 with B.

12           And I would suggest that you get the same result  
13 if you stick the word "with" in there instead of "and." If  
14 you say reacting A with B, that means that A and B need to  
15 be touching and reacting. It can't be A and then an  
16 intermediate and then B.

17           And so, I think that what this shows is that  
18 there is precedent, there is, you know, sort of -- a  
19 mainstream reading of this kind of claim is that the things  
20 that are reacting need to be in contact with one another.

21           And, you know, for -- and, of course, we also  
22 cited the *Lucin Technologies versus Gateway* case for the  
23 proposition that where we conclude the claim language as  
24 unambiguous, we have construed the claims to exclude all  
25 disclosed embodiments, right. So there are plenty of

1 examples.

2 And by the way, this -- when you look at the top  
3 of Column 14 where they talk about this reaction, it doesn't  
4 say this is the invention. It doesn't even say this is the  
5 preferred embodiment. It says in one example.

6 So I don't think we should, you know,  
7 overemphasize the example of the particular reagents that's  
8 given there. They have clearly written the claim designed  
9 for broader application, and they have written it in a way  
10 that is not exactly what they're now wishing it had been,  
11 but they are the masters of the claim and they ought to live  
12 with the claim that they have written.

13 And I guess that's really --

14 THE COURT: You agree --

15 MR. ROZENDAAL: -- our point.

16 THE COURT: -- that if I read it your way, Claim  
17 14 is gone; it's written out, right?

18 MR. ROZENDAAL: Well, I don't know that it's --  
19 I don't know that it's gone. I mean, I think it's a  
20 reaction that --

21 THE COURT: Well, I mean --

22 MR. ROZENDAAL: -- people would not want to do.

23 THE COURT: -- they wouldn't do it.

24 MR. ROZENDAAL: He said that doing that would  
25 have undesirable consequences.

1 THE COURT: I can't even -- you've got to give  
2 an inch here or you won't give anything?

3 You're not going to agree that that --

4 MR. ROZENDAAL: No, I agree --

5 THE COURT: So if I accept your construction, I  
6 have to read out Claim 14 of the patent?

7 MR. ROZENDAAL: Well, in the sense as a  
8 practical matter, yes, Your Honor.

9 THE COURT: Okay. And I have to read out the  
10 scheme five?

11 MR. ROZENDAAL: Scheme five would not be covered  
12 by this claim, that's right. That doesn't mean that they --  
13 I don't pretend to have looked at every single claim, but  
14 they all sort of point back to Claim 1 in one way or the  
15 other.

16 THE COURT: Well, because -- didn't your expert  
17 agree that the lithium reducing agent, I don't know the  
18 entire lithium, whatever it is, and the HCL a POSA would  
19 not --

20 MR. ROZENDAAL: He definitely said one would not  
21 want to put those particular reagents together. I certainly  
22 remember him saying that.

23 I guess my point is that he did not say that the  
24 claim is inoperative. He didn't say that this is a claim  
25 that becomes chemical gibberish.

1 THE COURT: I agree he did not say that.

2 All right. Leave the claim up, please.

3 I think the defendants are right. I think they  
4 have a better reading of this claim and I think it's really  
5 applying plain English. I don't even think it's ambiguous.  
6 And I think to read it the way the plaintiffs want would  
7 require me to completely ignore the word "contacting and."

8 The claim, the plain language of the claim  
9 requires that the carboxamide contact and react with two  
10 objects. They are joined by a conjunction. The first is a  
11 reducing agent and the second is an acid. But just because  
12 they're two doesn't mean they are sequential; and, in fact,  
13 to the opposite I conclude that the unambiguous language  
14 requires that the contact and reaction of a carboxamide with  
15 reducing agent and the acid occur simultaneously at the same  
16 time.

17 As I've gone through the grammar of the  
18 particular limitation, I think that it's very clear. I  
19 think any doubt is set aside by the fact that that  
20 limitation is concluded with a semicolon and followed by  
21 another limitation, which has a contacting and reacting  
22 limitation. It would not make sense -- that wouldn't be  
23 necessary if we could just have contacting and reacting  
24 apply to everything that follows. And I think, as counsel  
25 for plaintiff acknowledged, once the carboxamide has a

1 reaction or contact with the reducing agent, it's no longer  
2 the carboxamide. That is the subject of the clause.

3 So, I agree. And, look, the case law -- I'm not  
4 going to cite the case law. I'm familiar with the general  
5 principles. You've all cited and I have read the cases that  
6 you have cited, and I don't think it's going to add  
7 anything. And if -- I expect that you will cite the same  
8 cases to the Federal Circuit, and they are really there to  
9 set forth the principles that guide claim construction.

10 I am aware that this construction reads out an  
11 embodiment, principally -- or, namely, scheme five of the  
12 patent. I'm aware that it nullifies Claim 14. Based on  
13 extrinsic evidence, by the way, not by intrinsic evidence.

14 And when you construe a patent, you give  
15 priority to intrinsic evidence. You start with the claim, I  
16 did. You give meaning to the words of the claim, I did.  
17 And sometimes there are consequences that follow. The words  
18 are within the control of the patentee. And I think that's  
19 important.

20 And then lastly, as I alluded to before, the  
21 sixth example in the patent, in the text that describes it  
22 there's a step that does not use "contacting and." And so  
23 that would suggest that again there's something different  
24 between contacting and reacting, and I think that supports  
25 the construction that I've just made.

So this oral ruling will stand as my construction of the limitation. And I understand it will have consequences. All right.

All right. Is there anything else we need to address?

MR. GROOMBRIDGE: Your Honor, is the Court inclined to hear closings tomorrow?

THE COURT: What do you think? I mean, you see in a way I'd say yes because I've got a lot of fresh stuff in my head.

On the other hand, I'm not going to be able to, you know, reach decisions without briefing.

What are your thoughts?

MR. GROOMBRIDGE: I think that, you know, we have conferred previously and we were each of the view that it would probably be better to do briefing and then reconvene for whatever argument Your Honor wants. But, you know, we fully recognize that there is value to immediacy and recollection. And by the time we get back here it will be at least several weeks from now, I'm sure.

MR. ROZENDAAL: I agree with that, Your Honor.

Subject to the caveat that obviously we have an awful lot of smart lawyers here, I think we should do whatever the Court finds helpful.

THE COURT: Well, let's not have closing

1 argument. But let me just ask you some general questions,  
2 and I'm going to make a finding. I found Dr. Emens to be  
3 very credible. And just his mannerism while testifying, his  
4 directness and lack of hesitation. He does not appear to  
5 have any source of bias. And so, I found his testimony to  
6 be compelling. And when you brief, you should do that with  
7 that in mind because that's a factual finding that I'm  
8 making. And I'm making it today because I have had many  
9 days watching these witnesses, all of whom are very, very  
10 impressive, but his testimony in particular stuck out to me.  
11 So that's one thing.

12 Can we bring up -- let's just talk generally --  
13 and you can even be seated -- about just the idea that you  
14 can get a patent for a composition and then get a patent for  
15 a method to give that composition to certain patients.

16 That's just -- there's no question, right, that  
17 that's a patentable thing.

18 MR. GROOMBRIDGE: Absolutely, Your Honor, that's  
19 bedrock patent law.

20 THE COURT: Sure.

21 Go ahead, Mr. Rozendaal.

22 MR. ROZENDAAL: Well, if it is new, useful and  
23 nonobvious.

24 THE COURT: No, no, I totally get that, but what  
25 we do, most of these cases are methods.

1 MR. ROZENDAAL: Right. But I guess my point is  
2 that when one has a compound patent, often it's hard to show  
3 that the subsequent, the follow-on patents are new, useful  
4 and nonobvious.

5 THE COURT: Fair enough.

6 And I see these cases all the time. But I can't  
7 recall seeing a case where -- what I'll call, like, the next  
8 step occurs. Where we have a composition patent and then we  
9 get a patent for that composition with limitations that do  
10 nothing more than identify impurities in the composition.

11 Is that also patentable with the same surety  
12 that, you know, a method to give a -- that's novel, to give  
13 a drug to people is patentable.

14 MR. GROOMBRIDGE: I think so, Your Honor. And  
15 the reason is -- at least under the circumstances of this  
16 case. Because what we heard was because these are  
17 pharmaceuticals and they're regulated, and there's a whole  
18 lot of requirements about how you control for impurities and  
19 get them out of there, and that there is value to knowing  
20 the structures, right, therefore, what the -- there is  
21 utility to having done the work, which we heard on this  
22 record took several years, to identify these impurities so  
23 that the manufacturing process can then proceed more  
24 efficiently.

25 THE COURT: So was there any testimony that was



1 adduced that showed that the manufacturing process was  
2 actually affected by the identification of impurities?

3 MR. GROOMBRIDGE: Yes. I think there was  
4 testimony that the -- that it was easier for Apotex and Teva  
5 to satisfy FDA; that their processes were acceptable  
6 precisely because these five impurities have been identified  
7 and you could -- therefore, would not have to reinvent the  
8 wheel.

9 THE COURT: But that goes to getting approval by  
10 the FDA.

11 What I'm talking about, was there any evidence  
12 adduced that somebody altered their manufacturing process  
13 based on the identification of the impurities? I didn't  
14 hear anything.

15 MR. ROZENDAAL: I think the answer is no.

16 MR. GROOMBRIDGE: I'd have to go back and check,  
17 but I think the answer is yes. That Vanda, in the course of  
18 developing its process, went through iterations and used  
19 these -- this information to bring the process to a point  
20 where it would -- it was approvable by FDA.

21 THE COURT: I thought that the -- Teva's process  
22 was in 2013?

23 MR. GROOMBRIDGE: There's only ever been --  
24 well, I'm talking about what they did in the years of  
25 bringing it to the place where it could be initially

1 approved. I have no idea whether it's changed since then.

2 THE COURT: What year were the impurities  
3 identified?

4 MR. GROOMBRIDGE: The patent was filed in 2014.  
5 The testimony was that the work leading up to it was  
6 conducted over several years prior to that.

7 THE COURT: But when were the impurities -- I  
8 mean, at some point they had to have been identified.

9 MR. GROOMBRIDGE: I do not remember if there was  
10 a precise date, there may have been in Dr. Perni's  
11 testimony.

12 Ms. Young tells me -- and, again, I cannot  
13 represent to the Court that this is in the record -- but  
14 Ms. Young says Impurities 1 through 3 were identified in  
15 2011 and Impurities 5 and 6 were identified in 2013.

16 THE COURT: The process was finalized as of  
17 July 15, 2011?

18 MR. GROOMBRIDGE: No, I don't think so. The --

19 THE COURT: What was the date on the  
20 clinicaltrials.gov?

21 MR. GROOMBRIDGE: The clinicaltrials.gov is July  
22 of 2010.

23 THE COURT: '10, sorry.

24 MR. GROOMBRIDGE: That's the assertion, right.

25 THE COURT: Well, right.

1 But that's the process -- hasn't changed since  
2 then, right?

3 MR. GROOMBRIDGE: Absolutely it has. That --  
4 the way this would work, Your Honor, and I think there was  
5 testimony to this effect, at least in general, is when a  
6 pharmaceutical company is doing clinical work, it will make  
7 the drug often by one process, but as it's moving -- and  
8 that's what would be used in the patients in the clinical  
9 trial.

10 THE COURT: Right.

11 MR. GROOMBRIDGE: But then in parallel with  
12 that, as the process is moving, as the development is moving  
13 forward, you're trying to get a more rigorous process that  
14 you think you can get FDA approval, not for clinical trials  
15 but for actual full scale use. And that, you know, there  
16 are, you know, numerous people at pharmaceutical companies  
17 who are doing this.

18 THE COURT: When was that -- in this case when  
19 was that process, if there was any evidence at all about it  
20 then, when was that process approved by the FDA?

21 MR. GROOMBRIDGE: This was approved in early  
22 2014 as part of the approval for Hetlioz.

23 THE COURT: Okay.

24 MR. GROOMBRIDGE: And, you know, the way the  
25 thing works is that they put together an enormous package of

1 information that includes not -- you know, there's one  
2 section that's clinical studies, another section is  
3 manufacturing in tremendous detail precisely because these  
4 are things that are going to be taken by people. And that  
5 whole package is submitted to FDA, and there's some back and  
6 forth, and then eventually FDA will approve it, but only if  
7 all the pieces, each one individually, meet with approval.

8 THE COURT: Well, what I'd like you to do  
9 separate and apart from your briefing is just put together  
10 like a two-page letter that identifies in the record any  
11 evidence that the manufacturing process of tasimelteon was  
12 adjusted to account for the identification of the  
13 impurities. Because I didn't hear anything. And I don't  
14 mean -- I think the fact that you can more quickly obtain  
15 FDA approval because you happen to identify impurities,  
16 that's a different question it seems to me.

17 MR. GROOMBRIDGE: I guess, Your Honor, the way  
18 we would look at that is the question does the invention  
19 have utility. And if the utility is that it makes it easier  
20 to make a pure and more safe product, then that is a utility  
21 that meets the requirements of the patent laws.

22 THE COURT: All right. Well I still think, I  
23 think the problem I think for you all there is the process  
24 already was such that the limitations for the impurities  
25 could be met. And that's one thing. And then secondly, it

1 was disclosed in the Chinese patent that the aggregate of  
2 all the impurities was less than what the limitations  
3 require of any one impurity.

4 MR. GROOMBRIDGE: That --

5 THE COURT: Right.

6 MR. GROOMBRIDGE: Yes, but, I mean, then there's  
7 some testimony about how reliable is that, the optical  
8 rotation and the melting point.

9 THE COURT: Yeah, but you proffered that  
10 exhibit, right, it was your exhibit.

11 MR. GROOMBRIDGE: It was.

12 THE COURT: I just thought, you know -- like,  
13 for instance, I just didn't -- I'll make this a factual  
14 finding because, again, we're closer, it's better I do it.  
15 I didn't find the testimony from your expert to talk about  
16 the unreliability of that very credible.

17 Having put up the study, which right away puts  
18 the imprimatur of the expert on it, in my opinion, to then  
19 only when it becomes an issue to discount its legitimacy. I  
20 just didn't find it to be very credible.

21 MR. GROOMBRIDGE: I guess -- I'm not sure that  
22 it was we who proffered it, right. We mentioned it in the  
23 direct testimony.

24 THE COURT: Right. But it hadn't been  
25 introduced or mentioned in court prior to that; right?

1 MR. GROOMBRIDGE: Right. And the significance  
2 of it was that it was considered by the patent office, who,  
3 nonetheless, found the claims allowable over it.

4 THE COURT: Well, I can go back and look at it,  
5 but my reaction was I thought, I didn't -- I didn't find  
6 that very, very compelling testimony, but...

7 Okay. All right then, let's talk about  
8 briefing. You're going to go first on infringement, they  
9 get to respond, you go first on validity, you respond to  
10 them in the same day and I think we should move on it. I  
11 also would like a copy of the witnesses -- or pictures  
12 submitted to me so I can remember them weeks from now when I  
13 have to. Do we have a set of all the exhibits already?

14 MR. ROZENDAAL: I don't think we have the set  
15 yet, we have a list that we are finalizing for Your Honor.

16 THE COURT: Okay. And that's great. Just put  
17 them together. I'd like a hard copy with every exhibit with  
18 a file in order. And by "in order," I mean do plaintiff, do  
19 defendant, do joint in order.

20 So what's the schedule for briefing?

21 MR. GROOMBRIDGE: Would it make more sense if we  
22 confer and submit something to the Court?

23 THE COURT: Well, I think we should probably get  
24 a sense of what you were thinking first. For instance, I  
25 know you said December, I got -- I need to get this done in

1 the next couple of months.

2 MR. STONE: Your Honor is contemplating three  
3 rounds of briefing, we go first on infringement, they  
4 respond on both -- I guess you had said simultaneously but I  
5 suspect they need to read our infringement brief with  
6 respect to noninfringement.

7 MS. JACOBS: First on validity.

8 MR. STONE: Oh, I see. So them on validity at  
9 the same time as us on infringement a response and then a  
10 reply, I suppose?

11 THE COURT: Yes.

12 MR. STONE: So six briefs in total on three  
13 dates?

14 THE COURT: Yes.

15 MR. STONE: Is -- may we confer?

16 THE COURT: Yes. Look, here's where I look at  
17 it, that I really need it by the end of July. I mean at the  
18 absolute latest. I really need it before.

19 MS. JACOBS: Your Honor, if you could tell us  
20 when we need it by, I think we can confer --

21 THE COURT: So I need the reply brief -- hold on  
22 a second.

23 All right. I'll tell you part of the problem  
24 here I have an ANDA trial the last week of this month, I  
25 have two in June and one in July. So that's the problem.

1 And I also have two ANDAs I have got to write opinions for  
2 that I just finished and a bench trial for Ms. Jacobs that I  
3 have got to write.

4 (Discussion held off the record.)

5 THE COURT: So anyway, and I have got clerks  
6 turning over and I do not want to start with new clerks on  
7 an ANDA case. So can we get the reply briefs in May?

8 MR. ROZENDAAL: I think we can make that happen.

9 THE COURT: Okay. You know and frankly, look  
10 how many lawyers are in the room and look at this guy, he's  
11 the equivalent of all of you helping me, so...

12 So why don't we just do this, why don't you work  
13 backwards.

14 So May 27th, which is right before Memorial day  
15 weekend but I'll give you the whole month of May.

16 MS. JACOBS: We appreciate, Your Honor,  
17 understanding that today is April's Fools Day.

18 THE COURT: No, tomorrow day is, April fools.  
19 All right so that's it. And then no delays, no extensions;  
20 it's going to be May 27th, and that way your associates can  
21 have a Memorial Day weekend. In fact I'm going to make it  
22 Thursday. I'm going to make it Thursday, May 26th so the  
23 junior partners and the associates who the brunt of this  
24 will fall on will get it through.

25 Word limitations? You know, it's funny, the



1 best briefs, the best briefs are the shortest briefs. We're  
2 going to take care -- one of the patents is basically going  
3 to go away, right?

4 MR. GROOMBRIDGE: That's right, Your Honor, I  
5 mean it seems like that leads us to noninfringement on the  
6 '465.

7 THE COURT: Well, actually right, do they want  
8 to drop their invalidity?

9 MR. ROZENDAAL: That's the thing, I think we  
10 want to go ahead on the invalidity portion of it.

11 THE COURT: I'll warn you I did decide an ANDA  
12 case last year in August, I thought it was so slam dunk on  
13 infringement I didn't get to invalidity and there was  
14 another -- we tried invalidity and I reserved judgment --

15 (Discussion held off the record.)

16 THE COURT: Anyway, but I'm not guaranteeing you  
17 if you brief it, we'll see, I mean, I might, I might, so...  
18 I can't stress enough to prioritize your arguments. Pick  
19 your -- go with your best stuff first. I just can't stress  
20 that enough.

21 And so anything on the length?

22 (Discussion held off the record.)

23 MS. JACOBS: I will say that in the case we just  
24 finished with Judge Andrews last week the ANDA case we did  
25 60 pages per side total of 120 pages allocated among, you

1 know, all the briefing. Does Your Honor -- and I assume you  
2 want separate findings and briefing or what --

3 THE COURT: Is there a way to do that -- please  
4 have a seat. So let's think about this, let's be creative.  
5 We can go off the record.

6 (Discussion held off the record.)

7 THE COURT: All right. You're all going to  
8 confer about the briefing schedule, the reply brief will be  
9 due May 26th, the Thursday, I will not grant an extension.  
10 You need to work backwards to get the answering brief and  
11 opening brief dates. Each side will get an opening reply  
12 brief for the claims that it has brought. You didn't bring  
13 the declaration for noninfringement, did you? No. I'm  
14 combining you all between the defendants is one. And you  
15 can enter a -- or file a proposed stipulation and order with  
16 respect to briefing and page limitations next week, let's  
17 say close of business Friday.

18 At some point before the reply brief is  
19 submitted, you need to provide us a full set of exhibits.  
20 And if you can think of a creative way to have appendices  
21 with tabs and highlighted exhibits, I commend that to you,  
22 but don't require it. I'll leave that to you. You think it  
23 could facilitate our handling of the briefing, I commend  
24 you.

25 Review of the transcripts, we have got two court

1 reporters, so they will get rough transcripts out to you,  
2 you will -- and we'll enter an oral order with a date by  
3 which you must submit your errata. I will review my  
4 portions of the transcript at some point, and I don't know  
5 if it will be before you are given a rough draft or not. It  
6 probably will not, but... And so that -- I don't think that  
7 will affect you.

8 Can the defendants please submit a written  
9 order -- anything further you need to put in writing about  
10 my claim construction today?

11 MR. GROOMBRIDGE: I don't think so, Your Honor,  
12 I assumed that Your Honor was issuing the decision --

13 THE COURT: Well, I did issue the decision, but  
14 I often follow up with a written order because normally it's  
15 in the context of where the parties have submitted competing  
16 constructions and I pick that or I do another one. In this  
17 one, I didn't actually -- I did I think articulate  
18 specifically a construction, what I said was that the  
19 defendant's reading of the claim was correct and it requires  
20 that the reducing agent and acid be reacted with a  
21 carboxamide simultaneously, I think that's sufficient.

22 MR. GROOMBRIDGE: I think it's sufficient and  
23 I'm not sure what else the Court would do.

24 MR. ROZENDAAL: Yeah, I do wonder for future  
25 purposes if it might be cleaner just to have an order on the

1 docket that we could point to instead of having to point to  
2 a transcript. We're happy to take a crack at it.

3 THE COURT: All right. Why don't you submit  
4 something proposed. If you want, you can run it by each  
5 other or just submit it. Do that by Wednesday next week.

6 MR. ROZENDAAL: Yes, Your Honor.

7 THE COURT: All right. Okay. Are there any  
8 other matters? We'll issue an oral order with respect to  
9 the court reporter errata.

10 Anything else you can all think of?

11 MS. JACOBS: I alluded to this, Your Honor, but  
12 the parties will be filing a stipulation as to uncontested  
13 matters just so that the record is complete on that.

14 THE COURT: That would be good. And if you want  
15 to submit a Word version of that, I would appreciate it.

16 MR. ROZENDAAL: One other thing we are working  
17 on a stipulation of dismissal without prejudice and  
18 regarding the one patent that was dropped shortly before  
19 trial, so that should be appearing on the docket, I would  
20 think, shortly.

21 THE COURT: All right. Thank you. Okay.

22 Any other matters?

23 Well, thank you all. It was a very interesting  
24 trial, very well tried, very entertaining and interesting.  
25 And there are very, very interesting issues, that's for

1 sure, and they're important issues and we'll get to them as  
2 quickly as we can. Thank you.

3 (Whereupon, the following proceeding concluded  
4 at 3:44 p.m.)

5 I hereby certify the foregoing is a true  
6 and accurate transcript from my stenographic notes in the  
7 proceeding.

8 /s/ Michele L. Rolfe, RPR, CRR  
9 U.S. District Court  
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<b>\$</b>	<b>0.5</b> [2] - 1173:12, 1173:14	<b>12</b> [6] - 1079:25, 1089:25, 1124:11, 1125:4, 1131:7, 1235:19	1065:25, 1066:1, 1095:9, 1095:10, 1107:22, 1122:16, 1124:15, 1153:13, 1160:9, 1160:24, 1161:10, 1178:6, 1178:7, 1180:9, 1204:7, 1214:2, 1236:3, 1236:4, 1237:9, 1237:13, 1246:9, 1247:15, 1247:23, 1248:7	<b>22</b> [3] - 1008:6, 1021:24, 1181:12
<b>\$100,000</b> [1] - 1213:11	<b>01</b> [3] - 1023:14, 1024:2, 1025:6	<b>12-and-a-half</b> [1] - 1178:8		<b>23</b> [2] - 1021:24, 1124:13
<b>\$8,500</b> [2] - 1213:8, 1213:10	<b>1</b>	<b>12-hour</b> [1] - 1121:17		<b>24</b> [3] - 1183:8, 1192:9, 1200:23
<b>'</b>	<b>1</b> [28] - 1008:12, 1008:17, 1022:14, 1022:20, 1023:5, 1024:3, 1024:23, 1037:10, 1038:24, 1065:24, 1066:1, 1096:12, 1125:4, 1140:10, 1156:12, 1172:18, 1173:3, 1178:23, 1181:21, 1183:3, 1195:21, 1197:13, 1226:22, 1237:5, 1247:4, 1249:11, 1254:13, 1261:13	<b>120</b> [1] - 1268:24	<b>2.6</b> [1] - 1037:18	<b>24-hour</b> [8] - 1170:14, 1187:11, 1187:25, 1191:5, 1191:9, 1192:17, 1196:13, 1197:10
<b>'019</b> [8] - 1008:15, 1015:9, 1015:23, 1016:9, 1017:20, 1018:17, 1019:23, 1020:8	<b>1.100</b> [1] - 1027:22	<b>13</b> [6] - 1049:4, 1161:7, 1191:22, 1192:3, 1192:5, 1248:7	<b>2.75</b> [1] - 1177:11	<b>25</b> [9] - 1097:14, 1097:24, 1111:7, 1133:15, 1133:23, 1134:1, 1143:19, 1178:7, 1200:13
<b>'019</b> [4] - 1008:5, 1015:14, 1015:19, 1015:22	<b>1.1</b> [1] - 1037:18	<b>14</b> [27] - 1050:11, 1052:25, 1129:11, 1144:8, 1160:17, 1160:21, 1172:7, 1191:12, 1191:22, 1192:2, 1192:5, 1194:15, 1234:13, 1235:18, 1235:19, 1236:3, 1236:6, 1237:11, 1237:9, 1248:20, 1253:2, 1253:16, 1254:5, 1256:11	<b>20</b> [11] - 1015:3, 1094:25, 1095:13, 1180:13, 1194:6, 1196:15, 1196:25, 1197:7, 1205:12, 1205:19, 1211:2	<b>26th</b> [2] - 1267:21, 1269:8
<b>'10</b> [1] - 1261:22	<b>1.7</b> [1] - 1175:15	<b>15</b> [6] - 1010:5, 1010:18, 1010:23, 1017:22, 1235:20, 1261:16	<b>2000</b> [1] - 1042:16	<b>27th</b> [2] - 1267:13, 1267:19
<b>'244</b> [1] - 1184:8	<b>1.75-hour</b> [1] - 1175:15	<b>16</b> [5] - 1039:14, 1039:18, 1039:19, 1039:20, 1202:23	<b>2000s</b> [2] - 1218:15, 1218:18	<b>2:00</b> [1] - 1207:1
<b>'268</b> [3] - 1008:2, 1011:9, 1011:10	<b>10</b> [20] - 1006:19, 1007:16, 1008:13, 1008:25, 1020:11, 1020:15, 1020:18, 1020:20, 1020:25, 1047:1, 1073:15, 1076:11, 1152:9, 1152:12, 1152:13, 1207:4, 1210:9, 1226:21, 1226:23	<b>16.2</b> [1] - 1106:23	<b>2001</b> [1] - 1042:17	<b>2A6</b> [1] - 1114:24
<b>'384</b> [1] - 1059:10	<b>10-minute</b> [1] - 1126:8	<b>16.3</b> [1] - 1107:10	<b>2004</b> [5] - 1204:21, 1213:1, 1215:6, 1215:7, 1218:11	<b>2B6</b> [2] - 1114:24, 1115:23
<b>'465</b> [17] - 1006:19, 1007:4, 1007:16, 1008:13, 1009:1, 1012:21, 1013:2, 1015:17, 1020:11, 1020:15, 1020:18, 1020:20, 1021:10, 1226:21, 1227:6, 1228:13, 1268:5	<b>10.15</b> [1] - 1137:21	<b>17</b> [1] - 1199:11	<b>2007</b> [1] - 1042:18	<b>2C19</b> [4] - 1039:4, 1114:24, 1115:23, 1146:6
<b>'487</b> [2] - 1190:10, 1190:12	<b>10.20</b> [1] - 1141:3	<b>17.3</b> [1] - 1021:23	<b>2008</b> [2] - 1170:20, 1173:23	<b>2C8</b> [2] - 1114:24, 1115:23
<b>'529</b> [4] - 1010:10, 1010:14, 1010:19, 1010:24	<b>100-fold</b> [8] - 1045:9, 1045:11, 1045:12, 1045:22, 1176:19, 1177:2, 1178:19, 1218:12	<b>171</b> [1] - 1219:18	<b>2010</b> [6] - 1169:20, 1170:21, 1173:23, 1199:21, 1199:22, 1261:21	<b>2C9</b> [7] - 1066:8, 1067:25, 1069:18, 1074:1, 1103:8, 1114:21, 1146:6
<b>'604</b> [2] - 1191:4, 1227:11	<b>100-milligram</b> [4] - 1175:10, 1175:17, 1176:9, 1178:4	<b>18-651-CFC</b> [1] - 1:6	<b>2011</b> [2] - 1261:14, 1261:16	<b>2D6</b> [7] - 1066:8, 1067:25, 1069:18, 1073:25, 1103:8, 1114:21, 1146:6
<b>'70</b> [1] - 1026:14	<b>101</b> [1] - 1086:10	<b>1812</b> [1] - 1054:24	<b>2012</b> [23] - 1059:5, 1059:7, 1059:12, 1145:18, 1145:22, 1146:3, 1146:14, 1146:20, 1147:8, 1148:18, 1148:23, 1149:3, 1156:2, 1156:7, 1158:23, 1159:13, 1173:24, 1180:7, 1180:17, 1182:23, 1199:3, 1217:6	<b>2E1</b> [2] - 1114:24, 1115:23
<b>'70s</b> [1] - 1029:20	<b>102</b> [3] - 1086:9, 1086:10, 1089:25	<b>19</b> [1] - 1144:8	<b>2013</b> [2] - 1260:21, 1261:14	
<b>'72</b> [2] - 1026:14, 1026:18	<b>11</b> [6] - 1122:3, 1122:6, 1124:11, 1125:5, 1152:12	<b>1966</b> [1] - 1026:13	<b>2014</b> [3] - 1215:4, 1261:3, 1262:21	<b>3</b>
<b>'74</b> [1] - 1026:18	<b>11.25</b> [1] - 1200:14	<b>1970</b> [1] - 1026:13	<b>2015</b> [5] - 1171:15, 1172:10, 1199:17, 1199:19, 1218:3	<b>3</b> [19] - 1022:14, 1022:21, 1023:5, 1035:5, 1037:15, 1111:5, 1123:19, 1168:2, 1191:3, 1195:18, 1235:18, 1236:3, 1236:5, 1237:13, 1246:9, 1248:7, 1261:13
<b>'829</b> [6] - 1028:24, 1049:4, 1050:11, 1053:1, 1129:11, 1191:12	<b>11.6</b> [1] - 1166:13	<b>1970s</b> [1] - 1098:19	<b>2017</b> [2] - 1173:17, 1200:4	<b>30</b> [4] - 1032:4, 1123:19, 1207:25, 1208:4
<b>'910</b> [7] - 1029:2, 1050:20, 1050:21, 1053:19, 1129:13, 1140:3, 1140:7	<b>11:00</b> [5] - 1167:14, 1167:19, 1168:2, 1179:11, 1182:10	<b>1974</b> [1] - 1163:16	<b>2022</b> [1] - 1:16	<b>30(b)(6)</b> [1] - 1113:5
<b>'the</b> [1] - 1252:1	<b>11:40</b> [1] - 1126:8	<b>1978</b> [1] - 1164:18	<b>21</b> [2] - 1176:14, 1180:9	<b>301.37</b> [1] - 1006:16
<b>/</b>		<b>1981</b> [1] - 1163:18		<b>30th</b> [1] - 1251:21
<b>/s</b> [1] - 1272:7		<b>1999</b> [1] - 1127:23		<b>31</b> [2] - 1:16, 1125:1
<b>0</b>		<b>1A1</b> [5] - 1066:8, 1067:25, 1069:18, 1103:8, 1114:21		<b>32</b> [2] - 1020:1, 1124:11
<b>0.15</b> [2] - 1015:16, 1023:4		<b>1A2</b> [6] - 1067:20, 1067:21, 1069:17, 1073:25, 1096:13, 1100:14		
		<b>2</b>		
		<b>2</b> [26] - 1035:6, 1036:2,		

<p><b>32-minute</b> <sup>[1]</sup> - 1121:18</p> <p><b>34</b> <sup>[2]</sup> - 1020:1, 1125:6</p> <p><b>35</b> <sup>[2]</sup> - 1207:8, 1242:14</p> <p><b>36</b> <sup>[2]</sup> - 1007:20, 1124:13</p> <p><b>37</b> <sup>[1]</sup> - 1007:20</p> <p><b>38</b> <sup>[2]</sup> - 1111:9, 1111:10</p> <p><b>39</b> <sup>[1]</sup> - 1184:20</p> <p><b>39A</b> <sup>[1]</sup> - 1139:20</p> <p><b>3:44</b> <sup>[1]</sup> - 1272:3</p> <p><b>3A</b> <sup>[1]</sup> - 1096:13</p> <p><b>3A4</b> <sup>[15]</sup> - 1068:1, 1068:18, 1070:3, 1071:4, 1071:5, 1074:7, 1102:16, 1103:13, 1103:17, 1104:6, 1105:4, 1112:6, 1114:24, 1115:23, 1140:14</p>	<p>1147:2, 1147:4, 1148:1, 1178:6</p> <p><b>500</b> <sup>[1]</sup> - 1213:9</p> <p><b>52</b> <sup>[7]</sup> - 1008:5, 1008:16, 1019:25, 1082:18, 1082:25, 1226:6</p> <p><b>52(c)</b> <sup>[1]</sup> - 1221:22</p> <p><b>53</b> <sup>[6]</sup> - 1008:17, 1020:1, 1082:18, 1082:25, 1083:4, 1083:18</p> <p><b>55</b> <sup>[1]</sup> - 1120:5</p> <p><b>59</b> <sup>[2]</sup> - 1007:19, 1194:8</p> <p><b>599</b> <sup>[1]</sup> - 1251:22</p> <p><b>5:00</b> <sup>[1]</sup> - 1168:8</p>	<p><b>8-page</b> <sup>[1]</sup> - 1063:9</p> <p><b>80</b> <sup>[1]</sup> - 1046:15</p> <p><b>824</b> <sup>[1]</sup> - 1169:10</p> <p><b>830</b> <sup>[1]</sup> - 1014:7</p> <p><b>85</b> <sup>[2]</sup> - 1138:4, 1138:6</p> <p><b>867425</b> <sup>[1]</sup> - 1130:4</p> <p><b>87</b> <sup>[2]</sup> - 1138:5, 1138:7</p> <p><b>8:00</b> <sup>[1]</sup> - 1173:13</p> <p><b>8:30</b> <sup>[1]</sup> - 1006:4</p>	<p>1043:20, 1050:9, 1067:16, 1100:18, 1101:16, 1117:4, 1145:4, 1145:9, 1146:18, 1180:18, 1186:8, 1241:2, 1245:14, 1246:21, 1258:17, 1262:2</p> <p><b>absorption</b> <sup>[2]</sup> - 1030:15, 1030:20</p> <p><b>abstract</b> <sup>[1]</sup> - 1147:20</p> <p><b>abstracts</b> <sup>[1]</sup> - 1205:3</p> <p><b>abundance</b> <sup>[3]</sup> - 1084:15, 1085:19, 1216:15</p> <p><b>abundant</b> <sup>[2]</sup> - 1051:18, 1161:5</p> <p><b>Academy</b> <sup>[1]</sup> - 1217:19</p> <p><b>accept</b> <sup>[3]</sup> - 1103:1, 1110:25, 1254:4</p> <p><b>acceptable</b> <sup>[1]</sup> - 1260:4</p> <p><b>accepted</b> <sup>[1]</sup> - 1177:17</p> <p><b>according</b> <sup>[3]</sup> - 1008:8, 1011:10, 1125:3</p> <p><b>accords</b> <sup>[1]</sup> - 1244:25</p> <p><b>account</b> <sup>[2]</sup> - 1031:5, 1263:11</p> <p><b>accurate</b> <sup>[4]</sup> - 1021:19, 1021:20, 1171:10, 1272:5</p> <p><b>achieve</b> <sup>[2]</sup> - 1202:24, 1204:16</p> <p><b>achieved</b> <sup>[2]</sup> - 1192:12, 1194:11</p> <p><b>achievement</b> <sup>[1]</sup> - 1028:3</p> <p><b>achieving</b> <sup>[1]</sup> - 1198:11</p> <p><b>acid</b> <sup>[23]</sup> - 1007:12, 1020:14, 1021:4, 1021:6, 1226:24, 1229:14, 1234:12, 1234:25, 1235:21, 1236:6, 1236:17, 1237:10, 1237:12, 1243:8, 1249:22, 1250:17, 1250:21, 1250:22, 1251:3, 1255:10, 1255:14, 1270:19</p> <p><b>acknowledged</b> <sup>[1]</sup> - 1255:24</p> <p><b>act</b> <sup>[3]</sup> - 1035:11, 1078:5, 1121:24</p> <p><b>acting</b> <sup>[1]</sup> - 1102:13</p> <p><b>ACTION</b> <sup>[1]</sup> - 1:5</p> <p><b>action</b> <sup>[13]</sup> - 1026:23,</p>	<p>1028:25, 1035:10, 1037:7, 1037:14, 1040:10, 1040:16, 1048:6, 1104:20, 1109:21, 1110:12</p> <p><b>actions</b> <sup>[3]</sup> - 1014:8, 1069:14, 1110:2</p> <p><b>active</b> <sup>[6]</sup> - 1079:14, 1107:18, 1132:14, 1135:20, 1141:20, 1146:10</p> <p><b>activities</b> <sup>[3]</sup> - 1030:3, 1040:10, 1127:10</p> <p><b>activity</b> <sup>[10]</sup> - 1040:14, 1040:15, 1041:12, 1041:17, 1078:24, 1079:4, 1079:10, 1085:15, 1107:2, 1135:10</p> <p><b>acts</b> <sup>[1]</sup> - 1041:16</p> <p><b>actual</b> <sup>[9]</sup> - 1033:9, 1044:25, 1046:21, 1085:17, 1155:13, 1155:15, 1164:25, 1186:16, 1262:14</p> <p><b>actuality</b> <sup>[1]</sup> - 1059:25</p> <p><b>add</b> <sup>[7]</sup> - 1021:4, 1031:13, 1031:15, 1233:9, 1234:25, 1235:13, 1256:5</p> <p><b>adding</b> <sup>[3]</sup> - 1006:24, 1020:14, 1153:23</p> <p><b>addition</b> <sup>[1]</sup> - 1238:2</p> <p><b>additional</b> <sup>[2]</sup> - 1134:25, 1161:1</p> <p><b>address</b> <sup>[3]</sup> - 1113:20, 1227:25, 1257:4</p> <p><b>addressed</b> <sup>[1]</sup> - 1181:6</p> <p><b>addresses</b> <sup>[1]</sup> - 1199:4</p> <p><b>adduce</b> <sup>[1]</sup> - 1019:2</p> <p><b>adduced</b> <sup>[7]</sup> - 1017:19, 1017:21, 1017:22, 1017:25, 1224:19, 1259:25, 1260:11</p> <p><b>adjunct</b> <sup>[3]</sup> - 1126:20, 1127:23, 1128:3</p> <p><b>adjusted</b> <sup>[1]</sup> - 1263:11</p> <p><b>adjustment</b> <sup>[3]</sup> - 1091:17, 1098:5, 1098:11</p> <p><b>adjustments</b> <sup>[1]</sup> - 1119:20</p> <p><b>administer</b> <sup>[9]</sup> - 1048:15, 1059:16, 1084:18, 1100:22, 1117:8, 1118:7, 1178:19, 1179:25,</p>	
<p><b>4</b></p>	<p><b>6</b></p>	<p><b>9</b></p>	<p><b>9</b> <sup>[6]</sup> - 1019:14, 1122:16, 1149:19, 1196:11, 1219:18, 1228:7</p> <p><b>9.7</b> <sup>[1]</sup> - 1149:21</p> <p><b>90</b> <sup>[4]</sup> - 1076:12, 1115:12, 1134:15, 1148:1</p> <p><b>92</b> <sup>[1]</sup> - 1152:11</p> <p><b>98</b> <sup>[1]</sup> - 1148:15</p> <p><b>99.9</b> <sup>[9]</sup> - 1015:15, 1017:10, 1021:16, 1022:1, 1022:10, 1022:22, 1023:10, 1023:24, 1024:19</p> <p><b>9:00</b> <sup>[2]</sup> - 1173:7, 1173:15</p>	<p><b>absorption</b> <sup>[2]</sup> - 1030:15, 1030:20</p> <p><b>abstract</b> <sup>[1]</sup> - 1147:20</p> <p><b>abstracts</b> <sup>[1]</sup> - 1205:3</p> <p><b>abundance</b> <sup>[3]</sup> - 1084:15, 1085:19, 1216:15</p> <p><b>abundant</b> <sup>[2]</sup> - 1051:18, 1161:5</p> <p><b>Academy</b> <sup>[1]</sup> - 1217:19</p> <p><b>accept</b> <sup>[3]</sup> - 1103:1, 1110:25, 1254:4</p> <p><b>acceptable</b> <sup>[1]</sup> - 1260:4</p> <p><b>accepted</b> <sup>[1]</sup> - 1177:17</p> <p><b>according</b> <sup>[3]</sup> - 1008:8, 1011:10, 1125:3</p> <p><b>accords</b> <sup>[1]</sup> - 1244:25</p> <p><b>account</b> <sup>[2]</sup> - 1031:5, 1263:11</p> <p><b>accurate</b> <sup>[4]</sup> - 1021:19, 1021:20, 1171:10, 1272:5</p> <p><b>achieve</b> <sup>[2]</sup> - 1202:24, 1204:16</p> <p><b>achieved</b> <sup>[2]</sup> - 1192:12, 1194:11</p> <p><b>achievement</b> <sup>[1]</sup> - 1028:3</p> <p><b>achieving</b> <sup>[1]</sup> - 1198:11</p> <p><b>acid</b> <sup>[23]</sup> - 1007:12, 1020:14, 1021:4, 1021:6, 1226:24, 1229:14, 1234:12, 1234:25, 1235:21, 1236:6, 1236:17, 1237:10, 1237:12, 1243:8, 1249:22, 1250:17, 1250:21, 1250:22, 1251:3, 1255:10, 1255:14, 1270:19</p> <p><b>acknowledged</b> <sup>[1]</sup> - 1255:24</p> <p><b>act</b> <sup>[3]</sup> - 1035:11, 1078:5, 1121:24</p> <p><b>acting</b> <sup>[1]</sup> - 1102:13</p> <p><b>ACTION</b> <sup>[1]</sup> - 1:5</p> <p><b>action</b> <sup>[13]</sup> - 1026:23,</p>	<p><b>acts</b> <sup>[1]</sup> - 1041:16</p> <p><b>actual</b> <sup>[9]</sup> - 1033:9, 1044:25, 1046:21, 1085:17, 1155:13, 1155:15, 1164:25, 1186:16, 1262:14</p> <p><b>actuality</b> <sup>[1]</sup> - 1059:25</p> <p><b>add</b> <sup>[7]</sup> - 1021:4, 1031:13, 1031:15, 1233:9, 1234:25, 1235:13, 1256:5</p> <p><b>adding</b> <sup>[3]</sup> - 1006:24, 1020:14, 1153:23</p> <p><b>addition</b> <sup>[1]</sup> - 1238:2</p> <p><b>additional</b> <sup>[2]</sup> - 1134:25, 1161:1</p> <p><b>address</b> <sup>[3]</sup> - 1113:20, 1227:25, 1257:4</p> <p><b>addressed</b> <sup>[1]</sup> - 1181:6</p> <p><b>addresses</b> <sup>[1]</sup> - 1199:4</p> <p><b>adduce</b> <sup>[1]</sup> - 1019:2</p> <p><b>adduced</b> <sup>[7]</sup> - 1017:19, 1017:21, 1017:22, 1017:25, 1224:19, 1259:25, 1260:11</p> <p><b>adjunct</b> <sup>[3]</sup> - 1126:20, 1127:23, 1128:3</p> <p><b>adjusted</b> <sup>[1]</sup> - 1263:11</p> <p><b>adjustment</b> <sup>[3]</sup> - 1091:17, 1098:5, 1098:11</p> <p><b>adjustments</b> <sup>[1]</sup> - 1119:20</p> <p><b>administer</b> <sup>[9]</sup> - 1048:15, 1059:16, 1084:18, 1100:22, 1117:8, 1118:7, 1178:19, 1179:25,</p>
<p><b>4</b> <sup>[11]</sup> - 1036:1, 1038:23, 1045:6, 1049:17, 1050:21, 1053:18, 1111:5, 1122:4, 1124:12, 1129:13, 1140:3</p> <p><b>40</b> <sup>[3]</sup> - 1027:13, 1032:4, 1122:16</p> <p><b>41</b> <sup>[1]</sup> - 1114:12</p> <p><b>411</b> <sup>[1]</sup> - 1008:5</p> <p><b>43</b> <sup>[3]</sup> - 1114:14, 1156:12</p> <p><b>45</b> <sup>[7]</sup> - 1115:4, 1123:11, 1176:9, 1176:10, 1176:17, 1177:2, 1177:9</p> <p><b>450</b> <sup>[1]</sup> - 1075:11</p> <p><b>46</b> <sup>[2]</sup> - 1115:7, 1115:12</p> <p><b>48-hour</b> <sup>[2]</sup> - 1195:10, 1196:18</p> <p><b>49</b> <sup>[2]</sup> - 1164:17, 1186:11</p> <p><b>4:00</b> <sup>[1]</sup> - 1168:8</p> <p><b>4B</b> <sup>[1]</sup> - 1006:4</p>	<p><b>6</b> <sup>[9]</sup> - 1022:14, 1022:21, 1023:5, 1050:1, 1068:22, 1158:24, 1166:11, 1183:22, 1261:14</p> <p><b>6.10</b> <sup>[2]</sup> - 1080:10, 1080:11</p> <p><b>60</b> <sup>[3]</sup> - 1007:20, 1218:7, 1268:24</p> <p><b>602</b> <sup>[1]</sup> - 1251:22</p> <p><b>603</b> <sup>[1]</sup> - 1251:22</p> <p><b>61</b> <sup>[1]</sup> - 1007:7</p> <p><b>611</b> <sup>[1]</sup> - 1087:19</p> <p><b>614</b> <sup>[1]</sup> - 1087:20</p> <p><b>62</b> <sup>[1]</sup> - 1007:7</p> <p><b>63</b> <sup>[1]</sup> - 1006:21</p> <p><b>64</b> <sup>[2]</sup> - 1006:22, 1006:24</p> <p><b>65</b> <sup>[2]</sup> - 1138:4, 1138:7</p> <p><b>66</b> <sup>[1]</sup> - 1188:3</p> <p><b>67</b> <sup>[2]</sup> - 1219:5, 1251:21</p>	<p><b>9</b> <sup>[6]</sup> - 1019:14, 1122:16, 1149:19, 1196:11, 1219:18, 1228:7</p> <p><b>9.7</b> <sup>[1]</sup> - 1149:21</p> <p><b>90</b> <sup>[4]</sup> - 1076:12, 1115:12, 1134:15, 1148:1</p> <p><b>92</b> <sup>[1]</sup> - 1152:11</p> <p><b>98</b> <sup>[1]</sup> - 1148:15</p> <p><b>99.9</b> <sup>[9]</sup> - 1015:15, 1017:10, 1021:16, 1022:1, 1022:10, 1022:22, 1023:10, 1023:24, 1024:19</p> <p><b>9:00</b> <sup>[2]</sup> - 1173:7, 1173:15</p>	<p><b>absorption</b> <sup>[2]</sup> - 1030:15, 1030:20</p> <p><b>abstract</b> <sup>[1]</sup> - 1147:20</p> <p><b>abstracts</b> <sup>[1]</sup> - 1205:3</p> <p><b>abundance</b> <sup>[3]</sup> - 1084:15, 1085:19, 1216:15</p> <p><b>abundant</b> <sup>[2]</sup> - 1051:18, 1161:5</p> <p><b>Academy</b> <sup>[1]</sup> - 1217:19</p> <p><b>accept</b> <sup>[3]</sup> - 1103:1, 1110:25, 1254:4</p> <p><b>acceptable</b> <sup>[1]</sup> - 1260:4</p> <p><b>accepted</b> <sup>[1]</sup> - 1177:17</p> <p><b>according</b> <sup>[3]</sup> - 1008:8, 1011:10, 1125:3</p> <p><b>accords</b> <sup>[1]</sup> - 1244:25</p> <p><b>account</b> <sup>[2]</sup> - 1031:5, 1263:11</p> <p><b>accurate</b> <sup>[4]</sup> - 1021:19, 1021:20, 1171:10, 1272:5</p> <p><b>achieve</b> <sup>[2]</sup> - 1202:24, 1204:16</p> <p><b>achieved</b> <sup>[2]</sup> - 1192:12, 1194:11</p> <p><b>achievement</b> <sup>[1]</sup> - 1028:3</p> <p><b>achieving</b> <sup>[1]</sup> - 1198:11</p> <p><b>acid</b> <sup>[23]</sup> - 1007:12, 1020:14, 1021:4, 1021:6, 1226:24, 1229:14, 1234:12, 1234:25, 1235:21, 1236:6, 1236:17, 1237:10, 1237:12, 1243:8, 1249:22, 1250:17, 1250:21, 1250:22, 1251:3, 1255:10, 1255:14, 1270:19</p> <p><b>acknowledged</b> <sup>[1]</sup> - 1255:24</p> <p><b>act</b> <sup>[3]</sup> - 1035:11, 1078:5, 1121:24</p> <p><b>acting</b> <sup>[1]</sup> - 1102:13</p> <p><b>ACTION</b> <sup>[1]</sup> - 1:5</p> <p><b>action</b> <sup>[13]</sup> - 1026:23,</p>	<p><b>acts</b> <sup>[1]</sup> - 1041:16</p> <p><b>actual</b> <sup>[9]</sup> - 1033:9, 1044:25, 1046:21, 1085:17, 1155:13, 1155:15, 1164:25, 1186:16, 1262:14</p> <p><b>actuality</b> <sup>[1]</sup> - 1059:25</p> <p><b>add</b> <sup>[7]</sup> - 1021:4, 1031:13, 1031:15, 1233:9, 1234:25, 1235:13, 1256:5</p> <p><b>adding</b> <sup>[3]</sup> - 1006:24, 1020:14, 1153:23</p> <p><b>addition</b> <sup>[1]</sup> - 1238:2</p> <p><b>additional</b> <sup>[2]</sup> - 1134:25, 1161:1</p> <p><b>address</b> <sup>[3]</sup> - 1113:20, 1227:25, 1257:4</p> <p><b>addressed</b> <sup>[1]</sup> - 1181:6</p> <p><b>addresses</b> <sup>[1]</sup> - 1199:4</p> <p><b>adduce</b> <sup>[1]</sup> - 1019:2</p> <p><b>adduced</b> <sup>[7]</sup> - 1017:19, 1017:21, 1017:22, 1017:25, 1224:19, 1259:25, 1260:11</p> <p><b>adjunct</b> <sup>[3]</sup> - 1126:20, 1127:23, 1128:3</p> <p><b>adjusted</b> <sup>[1]</sup> - 1263:11</p> <p><b>adjustment</b> <sup>[3]</sup> - 1091:17, 1098:5, 1098:11</p> <p><b>adjustments</b> <sup>[1]</sup> - 1119:20</p> <p><b>administer</b> <sup>[9]</sup> - 1048:15, 1059:16, 1084:18, 1100:22, 1117:8, 1118:7, 1178:19, 1179:25,</p>	
<p><b>5</b></p>	<p><b>7</b></p>	<p><b>A</b></p>	<p><b>a-n-t-i-p-y-r-i-n-e</b> <sup>[1]</sup> - 1137:19</p> <p><b>a.m</b> <sup>[4]</sup> - 1006:4, 1167:14, 1167:19, 1179:11</p> <p><b>abbreviated</b> <sup>[1]</sup> - 1031:5</p> <p><b>abbreviation</b> <sup>[1]</sup> - 1107:3</p> <p><b>ability</b> <sup>[8]</sup> - 1079:17, 1098:10, 1098:14, 1131:3, 1143:1, 1167:8, 1189:25, 1190:6</p> <p><b>able</b> <sup>[18]</sup> - 1015:18, 1051:22, 1065:23, 1085:8, 1121:25, 1125:22, 1126:4, 1126:5, 1152:20, 1153:3, 1166:5, 1166:19, 1177:25, 1182:8, 1187:24, 1218:16, 1237:11, 1257:10</p> <p><b>absolute</b> <sup>[2]</sup> - 1111:14, 1266:17</p> <p><b>absolutely</b> <sup>[18]</sup> - 1022:15, 1041:24,</p>	<p><b>absorption</b> <sup>[2]</sup> - 1030:15, 1030:20</p> <p><b>abstract</b> <sup>[1]</sup> - 1147:20</p> <p><b>abstracts</b> <sup>[1]</sup> - 1205:3</p> <p><b>abundance</b> <sup>[3]</sup> - 1084:15, 1085:19, 1216:15</p> <p><b>abundant</b> <sup>[2]</sup> - 1051:18, 1161:5</p> <p><b>Academy</b> <sup>[1]</sup> - 1217:19</p> <p><b>accept</b> <sup>[3]</sup> - 1103:1, 1110:25, 1254:4</p> <p><b>acceptable</b> <sup>[1]</sup> - 1260:4</p> <p><b>accepted</b> <sup>[1]</sup> - 1177:17</p> <p><b>according</b> <sup>[3]</sup> - 1008:8, 1011:10, 1125:3</p> <p><b>accords</b> <sup>[1]</sup> - 1244:25</p> <p><b>account</b> <sup>[2]</sup> - 1031:5, 1263:11</p> <p><b>accurate</b> <sup>[4]</sup> - 1021:19, 1021:20, 1171:10, 1272:5</p> <p><b>achieve</b> <sup>[2]</sup> - 1202:24, 1204:16</p> <p><b>achieved</b> <sup>[2]</sup> - 1192:12, 1194:11</p> <p><b>achievement</b> <sup>[1]</sup> - 1028:3</p> <p><b>achieving</b> <sup>[1]</sup> - 1198:11</p> <p><b>acid</b> <sup>[23]</sup> - 1007:12, 1020:14, 1021:4, 1021:6, 1226:24, 1229:14, 1234:12, 1234:25, 1235:21, 1236:6, 1236:17, 1237:10, 1237:12, 1243:8, 1249:22, 1250:17, 1250:21, 1250:22, 1251:3, 1255:10, 1255:14, 1270:19</p> <p><b>acknowledged</b> <sup>[1]</sup> - 1255:24</p> <p><b>act</b> <sup>[3]</sup> - 1035:11, 1078:5, 1121:24</p> <p><b>acting</b> <sup>[1]</sup> - 1102:13</p> <p><b>ACTION</b> <sup>[1]</sup> - 1:5</p> <p><b>action</b> <sup>[13]</sup> - 1026:23,</p>	<p><b>acts</b> <sup>[1]</sup> - 1041:16</p> <p><b>actual</b> <sup>[9]</sup> - 1033:9, 1044:25, 1046:21, 1085:17, 1155:13, 1155:15, 1164:25, 1186:16, 1262:14</p> <p><b>actuality</b> <sup>[1]</sup> - 1059:25</p> <p><b>add</b> <sup>[7]</sup> - 1021:4, 1031:13, 1031:15, 1233:9, 1234:25, 1235:13, 1256:5</p> <p><b>adding</b> <sup>[3]</sup> - 1006:24, 1020:14, 1153:23</p> <p><b>addition</b> <sup>[1]</sup> - 1238:2</p> <p><b>additional</b> <sup>[2]</sup> - 1134:25, 1161:1</p> <p><b>address</b> <sup>[3]</sup> - 1113:20, 1227:25, 1257:4</p> <p><b>addressed</b> <sup>[1]</sup> - 1181:6</p> <p><b>addresses</b> <sup>[1]</sup> - 1199:4</p> <p><b>adduce</b> <sup>[1]</sup> - 1019:2</p> <p><b>adduced</b> <sup>[7]</sup> - 1017:19, 1017:21, 1017:22, 1017:25, 1224:19, 1259:25, 1260:11</p> <p><b>adjunct</b> <sup>[3]</sup> - 1126:20, 1127:23, 1128:3</p> <p><b>adjusted</b> <sup>[1]</sup> - 1263:11</p> <p><b>adjustment</b> <sup>[3]</sup> - 1091:17, 1098:5, 1098:11</p> <p><b>adjustments</b> <sup>[1]</sup> - 1119:20</p> <p><b>administer</b> <sup>[9]</sup> - 1048:15, 1059:16, 1084:18, 1100:22, 1117:8, 1118:7, 1178:19, 1179:25,</p>
<p><b>5</b> <sup>[6]</sup> - 1022:14, 1022:21, 1023:5, 1083:19, 1182:7, 1261:14</p> <p><b>50</b> <sup>[9]</sup> - 1027:4, 1032:4, 1123:12, 1146:16, 1146:22,</p>	<p><b>7</b> <sup>[6]</sup> - 1124:15, 1160:2, 1183:22, 1196:10, 1228:7, 1242:14</p> <p><b>7-to-9</b> <sup>[1]</sup> - 1166:18</p> <p><b>780</b> <sup>[1]</sup> - 1027:23</p> <p><b>79</b> <sup>[1]</sup> - 1146:5</p> <p><b>7:00</b> <sup>[5]</sup> - 1167:14, 1167:19, 1167:23, 1179:11, 1182:11</p>	<p><b>9</b> <sup>[6]</sup> - 1019:14, 1122:16, 1149:19, 1196:11, 1219:18, 1228:7</p> <p><b>9.7</b> <sup>[1]</sup> - 1149:21</p> <p><b>90</b> <sup>[4]</sup> - 1076:12, 1115:12, 1134:15, 1148:1</p> <p><b>92</b> <sup>[1]</sup> - 1152:11</p> <p><b>98</b> <sup>[1]</sup> - 1148:15</p> <p><b>99.9</b> <sup>[9]</sup> - 1015:15, 1017:10, 1021:16, 1022:1, 1022:10, 1022:22, 1023:10, 1023:24, 1024:19</p> <p><b>9:00</b> <sup>[2]</sup> - 1173:7, 1173:15</p>	<p><b>absorption</b> <sup>[2]</sup> - 1030:15, 1030:20</p> <p><b>abstract</b> <sup>[1]</sup> - 1147:20</p> <p><b>abstracts</b> <sup>[1]</sup> - 1205:3</p> <p><b>abundance</b> <sup>[3]</sup> - 1084:15, 1085:19, 1216:15</p> <p><b>abundant</b> <sup>[2]</sup> - 1051:18, 1161:5</p> <p><b>Academy</b> <sup>[1]</sup> - 1217:19</p> <p><b>accept</b> <sup>[3]</sup> - 1103:1, 1110:25, 1254:4</p> <p><b>acceptable</b> <sup>[1]</sup> - 1260:4</p> <p><b>accepted</b> <sup>[1]</sup> - 1177:17</p> <p><b>according&lt;/</b></p>		

<p>1190:6</p> <p><b>administered</b> [11] - 1042:1, 1059:19, 1079:11, 1079:13, 1134:12, 1170:25, 1174:2, 1174:4, 1179:14, 1180:14, 1202:8</p> <p><b>administering</b> [5] - 1057:17, 1059:18, 1103:23, 1182:6, 1189:21</p> <p><b>administers</b> [1] - 1204:17</p> <p><b>administration</b> [18] - 1051:2, 1067:18, 1070:9, 1100:12, 1100:19, 1172:24, 1176:11, 1180:17, 1181:21, 1181:24, 1184:17, 1190:3, 1196:25, 1197:6, 1200:5, 1200:16, 1218:15, 1220:20</p> <p><b>admiration</b> [1] - 1174:13</p> <p><b>admission</b> [3] - 1015:22, 1209:6, 1209:13</p> <p><b>admit</b> [1] - 1250:6</p> <p><b>admitted</b> [55] - 1014:10, 1014:11, 1026:5, 1026:7, 1026:8, 1032:20, 1032:21, 1035:3, 1036:25, 1037:2, 1037:3, 1038:1, 1038:11, 1038:14, 1038:15, 1042:23, 1042:25, 1043:1, 1044:7, 1044:9, 1044:10, 1048:23, 1048:25, 1049:1, 1071:23, 1071:24, 1095:23, 1095:24, 1099:16, 1099:19, 1127:19, 1127:20, 1136:14, 1137:12, 1139:23, 1139:24, 1139:25, 1144:20, 1151:6, 1151:7, 1162:5, 1162:6, 1169:12, 1169:13, 1170:2, 1170:3, 1171:25, 1172:1, 1182:20, 1185:22, 1185:23, 1209:16, 1209:17, 1219:12, 1219:13</p> <p><b>Admitted</b> [2] -</p>	<p>1136:13, 1137:11</p> <p><b>admonished</b> [1] - 1020:3</p> <p><b>advance</b> [7] - 1167:21, 1175:16, 1182:5, 1183:6, 1201:1, 1204:8, 1216:15</p> <p><b>advanced</b> [8] - 1100:25, 1101:3, 1118:8, 1167:21, 1167:25, 1183:16, 1201:7, 1202:9</p> <p><b>advancing</b> [3] - 1172:15, 1200:18, 1201:18</p> <p><b>advantage</b> [2] - 1066:1, 1211:3</p> <p><b>advantageous</b> [1] - 1190:1</p> <p><b>adverse</b> [3] - 1026:24, 1047:20, 1091:13</p> <p><b>advice</b> [4] - 1086:5, 1089:10, 1090:10, 1091:24</p> <p><b>advised</b> [1] - 1062:21</p> <p><b>advisor</b> [1] - 1213:5</p> <p><b>advisory</b> [5] - 1181:7, 1207:16, 1207:23, 1213:3, 1218:23</p> <p><b>advocate</b> [1] - 1240:6</p> <p><b>affect</b> [2] - 1138:12, 1270:6</p> <p><b>affected</b> [3] - 1132:11, 1140:14, 1260:1</p> <p><b>affinities</b> [1] - 1107:20</p> <p><b>affinity</b> [8] - 1035:14, 1037:13, 1040:16, 1048:6, 1107:12, 1108:2, 1110:11, 1142:2</p> <p><b>afraid</b> [1] - 1095:14</p> <p><b>afternoon</b> [5] - 1017:7, 1120:22, 1142:20, 1142:21, 1190:19</p> <p><b>age</b> [1] - 1106:5</p> <p><b>agent</b> [24] - 1007:12, 1020:13, 1021:3, 1021:8, 1154:16, 1226:24, 1234:10, 1234:24, 1235:14, 1236:5, 1237:8, 1237:12, 1243:8, 1249:25, 1250:1, 1250:7, 1250:9, 1250:13, 1251:1, 1254:16, 1255:10, 1255:14, 1255:25, 1270:19</p> <p><b>agents</b> [1] - 1236:19</p>	<p><b>aggregate</b> [4] - 1023:13, 1024:2, 1024:23, 1263:25</p> <p><b>ago</b> [3] - 1009:18, 1164:17, 1186:11</p> <p><b>agonist</b> [8] - 1039:5, 1062:5, 1204:18, 1208:25, 1209:1, 1210:2, 1211:13, 1211:20</p> <p><b>Agonist</b> [2] - 1072:5, 1159:25</p> <p><b>agree</b> [62] - 1007:3, 1009:6, 1010:14, 1013:1, 1024:7, 1024:24, 1024:25, 1052:15, 1062:2, 1067:2, 1069:23, 1071:12, 1083:1, 1086:23, 1094:19, 1096:2, 1129:16, 1145:14, 1145:21, 1146:3, 1146:12, 1146:19, 1147:1, 1147:2, 1147:7, 1148:6, 1148:12, 1148:18, 1149:3, 1150:25, 1151:18, 1155:7, 1155:19, 1156:1, 1156:6, 1156:16, 1156:20, 1174:12, 1174:14, 1189:18, 1191:2, 1195:25, 1197:22, 1198:14, 1198:22, 1209:8, 1217:10, 1228:12, 1229:3, 1230:16, 1242:2, 1245:6, 1247:6, 1250:3, 1250:23, 1253:13, 1254:2, 1254:3, 1254:16, 1254:25, 1256:2, 1257:20</p> <p><b>agreed</b> [5] - 1064:12, 1096:8, 1230:15, 1247:15, 1250:18</p> <p><b>agreement</b> [1] - 1228:21</p> <p><b>agrees</b> [2] - 1245:12, 1249:25</p> <p><b>ahead</b> [14] - 1006:15, 1015:5, 1019:8, 1074:4, 1089:22, 1225:3, 1225:22, 1228:19, 1233:24, 1233:25, 1240:17, 1249:10, 1258:20, 1268:9</p> <p><b>aimed</b> [1] - 1043:9</p>	<p><b>airplane</b> [1] - 1177:23</p> <p><b>al</b> [1] - 1:8</p> <p><b>aligned</b> [2] - 1185:5, 1239:24</p> <p><b>allocate</b> [1] - 1207:4</p> <p><b>allocated</b> [2] - 1122:1, 1268:24</p> <p><b>allow</b> [1] - 1016:4</p> <p><b>allowable</b> [1] - 1265:2</p> <p><b>allowed</b> [2] - 1053:12, 1237:4</p> <p><b>allowing</b> [1] - 1121:24</p> <p><b>allows</b> [3] - 1118:8, 1190:2, 1190:3</p> <p><b>alluded</b> [3] - 1228:22, 1256:19, 1271:10</p> <p><b>almost</b> [1] - 1232:17</p> <p><b>alone</b> [2] - 1044:17, 1046:11</p> <p><b>alpha</b> [1] - 1021:22</p> <p><b>alprazolam</b> [1] - 1029:22</p> <p><b>alter</b> [2] - 1041:17, 1047:18</p> <p><b>altered</b> [1] - 1260:11</p> <p><b>alters</b> [1] - 1041:5</p> <p><b>aluminum</b> [6] - 1021:4, 1234:11, 1234:24, 1235:14, 1236:5, 1236:17</p> <p><b>Ambien</b> [1] - 1030:1</p> <p><b>ambiguity</b> [1] - 1244:18</p> <p><b>ambiguous</b> [2] - 1251:17, 1255:4</p> <p><b>amend</b> [8] - 1016:3, 1017:24</p> <p><b>America</b> [3] - 1244:15, 1244:17, 1244:23</p> <p><b>American</b> [2] - 1027:18, 1217:19</p> <p><b>Amherst</b> [3] - 1026:13, 1052:12, 1063:16</p> <p><b>amount</b> [9] - 1032:7, 1041:13, 1041:19, 1051:9, 1105:14, 1116:18, 1124:25, 1132:5, 1164:7</p> <p><b>amounts</b> [3] - 1065:19, 1065:25, 1173:16</p> <p><b>amphetamines</b> [1] - 1187:22</p> <p><b>Analysis</b> [1] - 1094:6</p> <p><b>analysis</b> [20] - 1028:20, 1036:22, 1048:11, 1049:5, 1050:22, 1053:5, 1059:4, 1061:11, 1062:22, 1093:15,</p>	<p>1116:21, 1143:4, 1143:5, 1192:14, 1218:4, 1218:7, 1245:20, 1247:22</p> <p><b>analyze</b> [1] - 1028:22</p> <p><b>analyzed</b> [2] - 1106:10, 1140:8</p> <p><b>anchor</b> [7] - 1053:4, 1062:22, 1062:23, 1062:24, 1063:1, 1063:4, 1102:12</p> <p><b>AND</b> [1] - 1:3</p> <p><b>ANDA</b> [4] - 1266:23, 1267:6, 1268:10, 1268:23</p> <p><b>ANDAs</b> [2] - 1154:23, 1266:25</p> <p><b>ANDREW</b> [1] - 1126:11</p> <p><b>Andrew</b> [1] - 1120:19</p> <p><b>Andrews</b> [1] - 1268:23</p> <p><b>anhydride</b> [1] - 1021:6</p> <p><b>animal</b> [1] - 1040:18</p> <p><b>anogist</b> [1] - 1200:7</p> <p><b>answer</b> [41] - 1019:1, 1024:13, 1053:13, 1060:4, 1060:13, 1060:23, 1061:12, 1068:13, 1083:12, 1084:1, 1085:9, 1088:18, 1089:11, 1089:17, 1090:9, 1097:22, 1098:9, 1098:10, 1122:15, 1131:15, 1141:12, 1144:15, 1144:17, 1157:24, 1158:1, 1165:21, 1183:11, 1204:2, 1204:5, 1210:9, 1214:9, 1223:6, 1232:14, 1240:6, 1240:7, 1240:8, 1246:4, 1249:2, 1249:3, 1260:14, 1260:16</p> <p><b>answered</b> [3] - 1033:4, 1083:23, 1210:7</p> <p><b>answering</b> [2] - 1068:11, 1269:9</p> <p><b>answers</b> [1] - 1158:16</p> <p><b>anthropomorphize</b> [1] - 1078:9</p> <p><b>anti</b> [2] - 1154:2, 1154:8</p> <p><b>anti-tubercular</b> [2] - 1154:2, 1154:8</p> <p><b>antibiotics</b> [3] - 1075:21, 1075:23, 1075:24</p>
--	---	---	---	---



<p><b>anticipate</b> [1] - 1123:6</p> <p><b>anticipating</b> [1] - 1015:22</p> <p><b>anticipatory</b> [1] - 1015:24</p> <p><b>antidepressant</b> [2] - 1029:24, 1154:6</p> <p><b>antidepressants</b> [1] - 1154:2</p> <p><b>antifever</b> [1] - 1136:17</p> <p><b>antifungal</b> [2] - 1138:23, 1154:16</p> <p><b>antipyrene</b> [8] - 1136:7, 1136:16, 1136:21, 1136:24, 1137:16, 1137:17, 1138:4, 1138:12</p> <p><b>anyway</b> [5] - 1052:16, 1056:8, 1225:3, 1267:4, 1268:15</p> <p><b>anyways</b> [1] - 1119:3</p> <p><b>apart</b> [3] - 1211:6, 1212:21, 1263:8</p> <p><b>apologize</b> [10] - 1020:2, 1099:20, 1105:17, 1105:24, 1112:23, 1114:14, 1115:5, 1197:25, 1206:4, 1209:4</p> <p><b>Apotex</b> [3] - 1005:18, 1023:1, 1260:3</p> <p><b>apparent</b> [1] - 1201:20</p> <p><b>appeal</b> [1] - 1225:19</p> <p><b>appear</b> [4] - 1070:5, 1070:8, 1205:5, 1258:3</p> <p><b>appearance</b> [1] - 1134:2</p> <p><b>APPEARANCES</b> [1] - 1005:1</p> <p><b>appeared</b> [5] - 1034:20, 1039:21, 1146:9, 1161:14, 1182:14</p> <p><b>appearing</b> [2] - 1038:9, 1271:18</p> <p><b>appended</b> [1] - 1216:3</p> <p><b>appendices</b> [1] - 1269:19</p> <p><b>Appendix</b> [1] - 1251:22</p> <p><b>appendix</b> [1] - 1251:22</p> <p><b>applicable</b> [1] - 1171:4</p> <p><b>applicants</b> [1] - 1228:25</p> <p><b>application</b> [4] - 1008:4, 1008:9, 1163:25, 1253:8</p>	<p><b>applies</b> [1] - 1112:14</p> <p><b>apply</b> [4] - 1010:17, 1010:23, 1011:11, 1255:23</p> <p><b>applying</b> [2] - 1234:2, 1255:4</p> <p><b>appreciate</b> [5] - 1088:5, 1088:12, 1139:8, 1267:15, 1271:14</p> <p><b>approach</b> [4] - 1095:15, 1102:1, 1102:2, 1228:14</p> <p><b>approaching</b> [1] - 1057:13</p> <p><b>appropriate</b> [4] - 1014:16, 1016:3, 1088:22, 1226:13</p> <p><b>appropriately</b> [1] - 1121:25</p> <p><b>approvable</b> [1] - 1260:19</p> <p><b>approval</b> [10] - 1013:12, 1013:15, 1198:14, 1198:17, 1207:19, 1260:8, 1262:13, 1262:21, 1263:6, 1263:14</p> <p><b>approve</b> [3] - 1118:18, 1119:8, 1263:5</p> <p><b>approved</b> [12] - 1041:25, 1046:1, 1059:13, 1106:2, 1109:25, 1186:17, 1211:22, 1223:15, 1260:25, 1262:19, 1262:20</p> <p><b>April</b> [1] - 1267:17</p> <p><b>April's</b> [1] - 1267:16</p> <p><b>architecture</b> [1] - 1236:3</p> <p><b>area</b> [5] - 1090:3, 1110:9, 1186:20, 1188:25, 1201:11</p> <p><b>areas</b> [1] - 1154:21</p> <p><b>argument</b> [9] - 1018:10, 1121:17, 1125:1, 1224:18, 1227:25, 1243:6, 1244:5, 1257:16, 1257:25</p> <p><b>argument's</b> [1] - 1231:11</p> <p><b>arguments</b> [4] - 1125:9, 1247:9, 1247:10, 1268:17</p> <p><b>arithmetic</b> [2] - 1024:9, 1025:4</p> <p><b>arrive</b> [2] - 1006:25, 1008:22</p>	<p><b>arrow</b> [7] - 1044:21, 1046:14, 1173:3, 1173:4, 1179:2, 1232:25, 1234:18</p> <p><b>arrows</b> [1] - 1173:15</p> <p><b>ARSHT</b> [1] - 1005:12</p> <p><b>art</b> [64] - 1007:24, 1008:21, 1010:21, 1011:20, 1012:4, 1012:13, 1012:17, 1012:18, 1012:21, 1013:7, 1015:18, 1017:11, 1028:18, 1029:7, 1032:14, 1032:24, 1043:4, 1043:11, 1043:14, 1045:16, 1048:13, 1049:12, 1049:24, 1050:8, 1050:14, 1051:3, 1051:4, 1056:20, 1056:24, 1059:18, 1072:13, 1101:4, 1104:8, 1104:15, 1116:14, 1116:25, 1117:6, 1134:3, 1145:3, 1145:22, 1146:4, 1146:13, 1146:20, 1147:8, 1148:19, 1149:4, 1156:2, 1156:7, 1168:22, 1171:10, 1172:23, 1173:20, 1177:7, 1177:17, 1180:25, 1184:6, 1195:1, 1198:10, 1199:2, 1199:19, 1200:6, 1200:9, 1204:12, 1238:12</p> <p><b>article</b> [25] - 1034:19, 1038:8, 1038:19, 1038:21, 1054:25, 1061:19, 1062:4, 1063:14, 1070:8, 1072:3, 1072:8, 1099:6, 1103:3, 1103:16, 1113:23, 1113:24, 1170:8, 1170:21, 1173:4, 1183:2, 1199:17, 1199:19, 1199:21, 1199:22, 1200:4</p> <p><b>articles</b> [3] - 1042:12, 1042:14, 1146:9</p> <p><b>articulate</b> [1] - 1270:16</p> <p><b>artisan</b> [32] - 1024:17, 1054:3, 1060:4, 1060:8, 1060:13, 1060:17, 1061:7,</p>	<p>1061:8, 1061:11, 1068:24, 1074:11, 1092:8, 1092:13, 1092:18, 1098:3, 1101:9, 1101:21, 1102:9, 1104:4, 1105:4, 1109:15, 1111:20, 1129:17, 1130:7, 1130:10, 1132:2, 1134:9, 1134:18, 1135:7, 1138:13, 1140:20, 1141:5</p> <p><b>artisans</b> [1] - 1023:12</p> <p><b>ascertain</b> [1] - 1134:9</p> <p><b>ashamed</b> [1] - 1187:9</p> <p><b>aside</b> [3] - 1218:9, 1231:11, 1255:18</p> <p><b>asleep</b> [5] - 1168:8, 1179:23, 1187:4, 1228:4, 1228:7</p> <p><b>aspect</b> [1] - 1164:8</p> <p><b>aspects</b> [3] - 1049:3, 1050:21, 1172:12</p> <p><b>assay</b> [6] - 1066:17, 1092:20, 1100:7, 1100:11, 1101:10, 1176:3</p> <p><b>assays</b> [1] - 1097:2</p> <p><b>asserted</b> [8] - 1017:13, 1155:8, 1155:20, 1191:3, 1191:7, 1223:21</p> <p><b>assertion</b> [3] - 1188:5, 1189:14, 1261:23</p> <p><b>assess</b> [3] - 1135:1, 1135:8, 1159:9</p> <p><b>assessed</b> [4] - 1175:20, 1176:5, 1176:8, 1177:9</p> <p><b>assessing</b> [3] - 1133:19, 1177:6, 1223:7</p> <p><b>assessment</b> [2] - 1063:11, 1129:21</p> <p><b>Assessment</b> [1] - 1159:23</p> <p><b>assist</b> [2] - 1025:14, 1129:3</p> <p><b>assistant</b> [1] - 1128:2</p> <p><b>assisted</b> [1] - 1127:8</p> <p><b>associate</b> [1] - 1128:2</p> <p><b>associated</b> [2] - 1121:20, 1186:22</p> <p><b>associates</b> [2] - 1267:19, 1267:22</p> <p><b>assume</b> [3] - 1118:14, 1197:9, 1268:25</p> <p><b>assumed</b> [1] - 1270:11</p> <p><b>assumes</b> [1] - 1121:18</p>	<p><b>assuming</b> [1] - 1110:11</p> <p><b>assumptions</b> [1] - 1011:17</p> <p><b>Ativan</b> [1] - 1029:22</p> <p><b>atom</b> [1] - 1157:17</p> <p><b>atoms</b> [1] - 1157:16</p> <p><b>attempt</b> [1] - 1061:25</p> <p><b>attempts</b> [1] - 1186:12</p> <p><b>attention</b> [5] - 1015:8, 1025:24, 1031:4, 1165:17, 1209:5</p> <p><b>Attorney</b> [1] - 1203:12</p> <p><b>August</b> [1] - 1268:11</p> <p><b>authenticate</b> [1] - 1121:25</p> <p><b>authentication</b> [1] - 1121:20</p> <p><b>authenticity</b> [1] - 1125:1</p> <p><b>authors</b> [2] - 1072:8, 1113:19</p> <p><b>automatic</b> [1] - 1213:18</p> <p><b>automatically</b> [1] - 1213:19</p> <p><b>available</b> [18] - 1034:3, 1042:15, 1049:22, 1063:12, 1073:12, 1082:15, 1092:6, 1092:12, 1093:5, 1093:14, 1102:14, 1104:9, 1104:16, 1111:25, 1151:12, 1215:3, 1217:25, 1221:3</p> <p><b>average</b> [1] - 1167:12</p> <p><b>avoid</b> [13] - 1047:20, 1047:21, 1048:13, 1050:25, 1051:11, 1060:5, 1060:6, 1060:14, 1091:12, 1100:11, 1101:12, 1101:15</p> <p><b>avoidance</b> [1] - 1190:2</p> <p><b>avoided</b> [1] - 1051:10</p> <p><b>avoiding</b> [1] - 1140:11</p> <p><b>awake</b> [6] - 1165:7, 1166:22, 1166:23, 1166:24, 1167:5, 1187:6</p> <p><b>awakens</b> [1] - 1196:9</p> <p><b>awaking</b> [1] - 1203:2</p> <p><b>award</b> [1] - 1028:2</p> <p><b>awarded</b> [1] - 1028:2</p> <p><b>awards</b> [2] - 1027:25, 1028:1</p> <p><b>aware</b> [21] - 1011:21, 1012:5, 1012:16, 1012:17, 1013:20,</p>
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1043:11, 1117:1, 1138:13, 1181:23, 1184:15, 1188:2, 1188:4, 1188:15, 1199:2, 1210:19, 1211:6, 1212:2, 1217:25, 1227:12, 1256:9, 1256:11 <b>awareness</b> [1] - 1150:6 <b>awful</b> [1] - 1257:21 <b>axis</b> [1] - 1201:11	1244:16 <b>battle</b> [1] - 1202:24 <b>bear</b> [1] - 1156:15 <b>beast</b> [1] - 1015:4 <b>beating</b> [1] - 1077:4 <b>became</b> [1] - 1203:9 <b>becomes</b> [6] - 1030:13, 1239:8, 1243:14, 1247:11, 1254:24, 1264:18 <b>bed</b> [4] - 1179:13, 1179:24, 1182:11, 1185:25 <b>bedrock</b> [1] - 1258:18 <b>bedtime</b> [15] - 1172:18, 1172:20, 1173:19, 1174:5, 1176:7, 1180:14, 1181:21, 1182:7, 1182:10, 1183:3, 1196:16, 1197:1, 1197:7, 1203:7, 1211:2 <b>BEFORE</b> [1] - 1:19 <b>began</b> [4] - 1164:17, 1164:19, 1176:16 <b>begin</b> [4] - 1171:8, 1172:19, 1233:4, 1233:9 <b>beginning</b> [10] - 1006:4, 1096:4, 1167:25, 1172:17, 1172:19, 1178:25, 1179:3, 1232:9, 1234:17, 1242:23 <b>begins</b> [4] - 1053:5, 1159:2, 1203:8, 1241:4 <b>begun</b> [1] - 1120:15 <b>behalf</b> [3] - 1126:12, 1127:5, 1215:10 <b>behavior</b> [1] - 1150:7 <b>believes</b> [2] - 1024:18, 1144:25 <b>bell</b> [1] - 1204:22 <b>below</b> [6] - 1011:3, 1095:9, 1096:20, 1181:2, 1201:10, 1202:11 <b>bench</b> [5] - 1006:3, 1020:22, 1117:16, 1216:20, 1267:1 <b>Bench</b> [1] - 1:16 <b>beneficial</b> [1] - 1078:22 <b>benefit</b> [6] - 1088:9, 1099:17, 1188:6, 1189:4, 1189:6, 1189:15 <b>benefits</b> [2] - 1033:14,	1132:8 <b>benzodiazapine</b> [1] - 1029:21 <b>berate</b> [1] - 1187:6 <b>berating</b> [2] - 1187:4, 1187:10 <b>Bergmeier</b> [11] - 1006:6, 1006:9, 1013:25, 1015:14, 1016:12, 1019:17, 1019:20, 1020:7, 1023:23, 1037:5, 1211:5 <b>Bergmeier's</b> [1] - 1015:7 <b>best</b> [6] - 1059:5, 1156:14, 1165:12, 1267:25, 1268:18 <b>better</b> [8] - 1079:8, 1104:22, 1241:19, 1246:4, 1249:1, 1255:3, 1257:15, 1264:13 <b>between</b> [38] - 1016:16, 1021:9, 1045:25, 1051:24, 1060:6, 1060:7, 1060:10, 1060:14, 1060:19, 1063:17, 1076:7, 1085:23, 1086:1, 1086:5, 1089:9, 1089:20, 1090:7, 1090:15, 1090:23, 1090:24, 1092:13, 1092:15, 1105:23, 1108:16, 1115:21, 1116:14, 1117:2, 1117:10, 1123:17, 1155:9, 1155:21, 1167:19, 1176:4, 1214:1, 1236:9, 1246:23, 1256:23, 1269:13 <b>beyond</b> [4] - 1110:9, 1125:20, 1158:4, 1158:12 <b>bias</b> [1] - 1258:4 <b>bibliography</b> [1] - 1071:11 <b>big</b> [4] - 1090:11, 1090:14, 1118:22, 1246:1 <b>bigger</b> [1] - 1240:3 <b>biggest</b> [1] - 1240:4 <b>bile</b> [2] - 1076:4, 1133:5 <b>biliary</b> [1] - 1133:6 <b>bind</b> [4] - 1040:16, 1110:6, 1110:10, 1110:15	<b>binder</b> [27] - 1025:24, 1033:24, 1034:14, 1036:17, 1037:20, 1063:6, 1063:7, 1071:15, 1082:18, 1094:3, 1099:4, 1126:16, 1127:12, 1136:3, 1136:25, 1144:5, 1147:14, 1149:8, 1150:17, 1159:17, 1169:1, 1171:12, 1191:14, 1191:16, 1191:18, 1205:6, 1208:2 <b>binders</b> [1] - 1121:1 <b>binding</b> [7] - 1035:12, 1035:14, 1035:18, 1048:6, 1107:12, 1107:20, 1110:8 <b>binds</b> [3] - 1037:13, 1107:17, 1210:2 <b>bioavailability</b> [3] - 1111:2, 1111:6, 1111:14 <b>biochemistry</b> [1] - 1163:16 <b>biological</b> [1] - 1167:3 <b>biology</b> [1] - 1163:15 <b>biomedical</b> [8] - 1027:11, 1034:20, 1038:9, 1039:20, 1047:19, 1047:21, 1106:12, 1117:9 <b>bit</b> [11] - 1021:15, 1021:21, 1037:10, 1041:1, 1085:2, 1125:20, 1135:21, 1157:12, 1157:13, 1165:13, 1190:23 <b>BLAKE</b> [1] - 1005:16 <b>blank</b> [1] - 1048:4 <b>blind</b> [17] - 1164:21, 1167:4, 1168:14, 1171:4, 1180:7, 1183:7, 1183:23, 1186:21, 1186:25, 1187:3, 1187:10, 1190:24, 1202:6, 1203:16, 1217:16, 1218:8, 1218:16 <b>blindness</b> [1] - 1186:22 <b>blocking</b> [2] - 1222:2, 1222:14 <b>blood</b> [7] - 1030:20, 1030:22, 1041:14, 1041:21, 1134:13, 1175:4, 1185:7 <b>bloodstream</b> [1] - 1176:1	<b>blue</b> [9] - 1044:21, 1044:22, 1046:14, 1087:7, 1087:9, 1087:11, 1173:3, 1173:4, 1234:24 <b>Blyden</b> [1] - 1137:3 <b>BMS</b> [14] - 1009:17, 1010:10, 1064:25, 1069:18, 1071:8, 1074:12, 1081:11, 1105:2, 1112:3, 1112:12, 1112:15, 1113:3, 1113:7, 1114:17 <b>BMS's</b> [2] - 1009:17, 1112:6 <b>BMS-214778</b> [2] - 1072:4, 1073:22 <b>board</b> [5] - 1185:12, 1212:7, 1212:8, 1213:3, 1213:4 <b>board-certified</b> [1] - 1212:7 <b>boards</b> [1] - 1027:16 <b>body</b> [17] - 1075:6, 1075:18, 1076:3, 1076:23, 1079:8, 1080:18, 1081:17, 1097:19, 1111:12, 1133:1, 1133:2, 1134:16, 1135:24, 1138:19, 1139:7, 1143:20, 1233:7 <b>boils</b> [1] - 1229:9 <b>bond</b> [1] - 1052:12 <b>book</b> [1] - 1043:25 <b>borane</b> [1] - 1021:7 <b>borohydride</b> [3] - 1020:13, 1020:16, 1021:5 <b>Boston</b> [2] - 1026:17 <b>bother</b> [1] - 1119:15 <b>bottom</b> [21] - 1006:21, 1007:20, 1008:16, 1034:5, 1035:5, 1050:1, 1057:5, 1064:3, 1064:4, 1098:4, 1106:22, 1107:9, 1115:12, 1131:9, 1133:11, 1149:18, 1151:9, 1205:3, 1205:4, 1236:10, 1241:23 <b>bought</b> [1] - 1244:4 <b>bound</b> [1] - 1034:6 <b>boundary</b> [1] - 1045:21 <b>bowel</b> [3] - 1030:15, 1030:16, 1030:18 <b>bowl</b> [1] - 1185:11
---	---	--	--	---

<p><b>box</b> [1] - 1134:7  <b>boxes</b> [1] - 1082:22  <b>brackets</b> [1] - 1021:22  <b>brain</b> [5] - 1025:6,  1035:13, 1056:9,  1107:18, 1203:1  <b>brand</b> [2] - 1221:6,  1221:10  <b>break</b> [10] - 1019:15,  1079:20, 1079:22,  1080:5, 1125:12,  1126:8, 1205:13,  1206:15, 1207:11,  1248:12  <b>breaker</b> [1] - 1248:25  <b>breaking</b> [1] - 1017:5  <b>breakthrough</b> [2] -  1118:24, 1119:17  <b>brief</b> [15] - 1116:5,  1123:3, 1123:4,  1215:20, 1225:2,  1226:12, 1258:5,  1266:4, 1266:20,  1268:16, 1269:7,  1269:9, 1269:10,  1269:11, 1269:17  <b>briefing</b> [12] -  1227:20, 1257:11,  1257:15, 1263:8,  1265:7, 1265:19,  1266:2, 1268:25,  1269:1, 1269:7,  1269:15, 1269:22  <b>briefly</b> [9] - 1026:10,  1028:14, 1028:21,  1048:10, 1048:21,  1056:7, 1163:13,  1184:19, 1212:19  <b>briefs</b> [5] - 1266:11,  1267:6, 1267:25  <b>Brigham</b> [1] - 1163:10  <b>bring</b> [20] - 1018:13,  1025:17, 1026:10,  1038:16, 1039:18,  1063:24, 1069:5,  1096:19, 1106:19,  1113:14, 1114:13,  1114:15, 1166:10,  1179:23, 1191:11,  1238:12, 1258:11,  1260:18, 1269:11  <b>bringing</b> [1] - 1260:24  <b>Bristol</b> [4] - 1036:15,  1072:9, 1113:20,  1211:11  <b>Bristol-Myers</b> [4] -  1036:15, 1072:9,  1113:20, 1211:11  <b>Britannica</b> [1] -  1054:23</p>	<p><b>broaden</b> [1] - 1245:18  <b>broader</b> [1] - 1253:8  <b>broadly</b> [2] - 1034:18,  1038:19  <b>brochure</b> [1] - 1114:4  <b>broke</b> [2] - 1080:9,  1080:14  <b>broken</b> [3] - 1076:8,  1111:12, 1133:7  <b>Bronx</b> [1] - 1026:16  <b>brooks</b> [6] - 1025:17,  1038:17, 1147:15,  1149:9, 1156:11,  1249:10  <b>brought</b> [5] - 1016:1,  1018:12, 1187:14,  1209:5, 1269:11  <b>brunt</b> [1] - 1267:22  <b>BRYON</b> [1] - 1005:4  <b>bucket</b> [2] - 1241:6,  1243:1  <b>bucks</b> [1] - 1246:2  <b>building</b> [1] - 1206:20  <b>bullet</b> [1] - 1158:24  <b>bunch</b> [2] - 1107:6,  1108:25  <b>Burgess</b> [4] - 1169:21,  1171:15, 1199:21,  1199:22  <b>Burgess's</b> [1] -  1170:20  <b>business</b> [1] -  1269:16  <b>busting</b> [1] - 1056:2  <b>but..</b> [3] - 1084:9,  1265:5, 1270:5  <b>butchered</b> [1] - 1153:1  <b>buy</b> [1] - 1139:13  <b>BY</b> [91] - 1005:3,  1005:8, 1005:12,  1005:15, 1006:8,  1019:19, 1020:6,  1021:1, 1025:9,  1025:19, 1026:9,  1028:12, 1032:22,  1034:12, 1035:4,  1035:25, 1037:4,  1038:6, 1038:18,  1043:2, 1044:11,  1045:2, 1049:2,  1052:8, 1058:16,  1061:18, 1064:1,  1064:17, 1069:6,  1072:2, 1073:16,  1073:20, 1080:13,  1089:6, 1089:23,  1095:2, 1096:1,  1096:21, 1099:9,  1099:21, 1106:21,  1107:11, 1111:1,</p>	<p>1113:16, 1114:16,  1116:7, 1126:15,  1127:21, 1129:7,  1129:24, 1130:23,  1132:22, 1134:24,  1136:15, 1137:13,  1137:22, 1139:3,  1140:1, 1140:6,  1140:19, 1141:4,  1142:19, 1147:16,  1150:16, 1151:8,  1155:6, 1156:13,  1157:14, 1158:19,  1159:19, 1163:5,  1165:15, 1166:15,  1169:14, 1170:6,  1172:8, 1180:5,  1186:1, 1188:12,  1190:18, 1191:24,  1207:14, 1208:1,  1209:7, 1209:18,  1210:11, 1211:19,  1214:14, 1216:25,  1219:14, 1220:17</p>	<p>1270:20  <b>care</b> [5] - 1113:9,  1132:2, 1135:7,  1212:8, 1268:1  <b>career</b> [2] - 1164:9,  1164:12  <b>carefully</b> [1] - 1022:24  <b>carried</b> [4] - 1021:14,  1198:18, 1208:11,  1237:14  <b>carry</b> [5] - 1006:18,  1007:25, 1008:6,  1008:18, 1195:11  <b>cartoon</b> [1] - 1173:15  <b>case</b> [62] - 1007:18,  1013:21, 1028:23,  1056:21, 1057:6,  1059:17, 1072:23,  1080:2, 1094:16,  1101:6, 1118:11,  1120:10, 1120:11,  1120:12, 1122:17,  1124:2, 1131:18,  1137:6, 1164:10,  1167:17, 1169:23,  1173:25, 1175:2,  1176:3, 1184:16,  1188:16, 1192:24,  1192:25, 1194:10,  1198:6, 1198:9,  1205:17, 1209:9,  1216:4, 1221:18,  1223:10, 1223:12,  1224:7, 1224:11,  1224:12, 1225:17,  1230:21, 1233:11,  1233:17, 1235:21,  1237:22, 1244:11,  1244:15, 1246:6,  1250:21, 1251:20,  1251:23, 1252:21,  1256:2, 1256:3,  1259:6, 1259:15,  1262:17, 1267:6,  1268:11, 1268:22,  1268:23  <b>cases</b> [16] - 1040:23,  1086:7, 1088:16,  1089:11, 1089:18,  1146:16, 1146:23,  1147:2, 1147:4,  1154:22, 1192:18,  1237:21, 1256:4,  1256:7, 1258:24,  1259:5  <b>cat</b> [1] - 1202:22  <b>catalyze</b> [1] - 1078:11  <b>caused</b> [2] - 1078:13,  1140:11  <b>causes</b> [2] - 1116:18,</p>	<p>1152:5  <b>causing</b> [1] - 1041:6  <b>caution</b> [18] - 1049:25,  1050:6, 1050:18,  1069:20, 1069:25,  1070:3, 1070:10,  1101:13, 1101:15,  1101:18, 1101:23,  1103:10, 1103:12,  1103:22, 1118:23,  1119:19, 1153:23,  1216:16  <b>cautionary</b> [1] -  1118:12  <b>cautions</b> [2] -  1067:11, 1067:18  <b>cautious</b> [1] - 1102:3  <b>caveat</b> [1] - 1257:21  <b>cell</b> [4] - 1065:6,  1065:20, 1114:18  <b>cells</b> [4] - 1065:7,  1065:14, 1065:17,  1066:3  <b>Center</b> [3] - 1026:17,  1126:21, 1127:24  <b>centers</b> [2] - 1157:25,  1219:19  <b>central</b> [1] - 1117:7  <b>centrifuge</b> [2] -  1034:4, 1034:8  <b>CEO</b> [1] - 1126:21  <b>certain</b> [6] - 1067:19,  1135:23, 1216:14,  1216:21, 1244:21,  1258:14  <b>certainly</b> [18] -  1012:10, 1024:5,  1024:25, 1028:10,  1062:11, 1062:12,  1064:13, 1087:3,  1102:1, 1106:9,  1109:14, 1111:22,  1192:21, 1195:4,  1208:23, 1236:18,  1242:9, 1254:20  <b>certification</b> [1] -  1220:24  <b>certified</b> [3] - 1212:7,  1212:8, 1221:6  <b>certify</b> [1] - 1272:4  <b>cetera</b> [2] - 1034:3,  1042:12  <b>chairman</b> [1] - 1213:2  <b>chance</b> [1] - 1158:10  <b>change</b> [9] - 1045:19,  1078:13, 1091:11,  1091:12, 1092:2,  1135:13, 1135:14,  1135:16, 1146:24  <b>changed</b> [3] -</p>
---	---	---	---	---

<p>1231:16, 1260:25, 1261:25</p> <p><b>changes</b> [1] - 1091:23</p> <p><b>changing</b> [1] - 1091:4</p> <p><b>chapter</b> [1] - 1043:25</p> <p><b>characteristic</b> [1] - 1190:25</p> <p><b>characteristics</b> [1] - 1142:1</p> <p><b>charge</b> [1] - 1135:18</p> <p><b>Charles</b> [3] - 1162:20, 1163:8, 1208:7</p> <p><b>CHARLES</b> [1] - 1162:21</p> <p><b>chart</b> [8] - 1040:9, 1096:3, 1096:7, 1096:8, 1096:22, 1097:5, 1101:22, 1124:10</p> <p><b>check</b> [2] - 1023:1, 1260:15</p> <p><b>Chef</b> [3] - 1244:15, 1244:17, 1244:23</p> <p><b>chemical</b> [4] - 1083:10, 1233:8, 1250:1, 1254:24</p> <p><b>chemically</b> [1] - 1229:2</p> <p><b>Chief</b> [1] - 1:19</p> <p><b>chief</b> [3] - 1027:13, 1027:14, 1163:8</p> <p><b>child</b> [1] - 1187:2</p> <p><b>children</b> [1] - 1187:10</p> <p><b>Chinese</b> [4] - 1008:4, 1015:8, 1017:20, 1263:25</p> <p><b>chiral</b> [1] - 1157:25</p> <p><b>chloride</b> [4] - 1006:25, 1235:22, 1236:19, 1237:10</p> <p><b>chop</b> [1] - 1078:9</p> <p><b>chromatographic</b> [1] - 1022:17</p> <p><b>chronological</b> [1] - 1178:16</p> <p><b>cigarette</b> [1] - 1161:18</p> <p><b>Cipro</b> [1] - 1149:5</p> <p><b>circadian</b> [23] - 1062:6, 1163:1, 1163:25, 1164:2, 1164:14, 1165:17, 1166:5, 1167:20, 1174:25, 1177:20, 1178:1, 1183:14, 1184:22, 1185:2, 1192:1, 1194:20, 1200:23, 1201:19, 1202:20, 1202:25, 1203:18, 1217:15</p> <p><b>Circadian</b> [1] - 1163:9</p>	<p><b>Circuit</b> [3] - 1228:24, 1252:7, 1256:7</p> <p><b>circulating</b> [3] - 1178:6, 1178:8, 1178:9</p> <p><b>circulation</b> [4] - 1030:21, 1030:22, 1030:25, 1111:16</p> <p><b>circumstances</b> [3] - 1091:19, 1091:21, 1259:14</p> <p><b>citation</b> [4] - 1130:4, 1160:21, 1161:7, 1185:17</p> <p><b>citations</b> [1] - 1130:5</p> <p><b>cite</b> [4] - 1036:12, 1200:4, 1256:3, 1256:6</p> <p><b>cited</b> [5] - 1052:19, 1251:20, 1252:21, 1256:4, 1256:5</p> <p><b>cites</b> [1] - 1160:17</p> <p><b>citing</b> [3] - 1069:18, 1071:9, 1071:13</p> <p><b>City</b> [1] - 1026:17</p> <p><b>city</b> [1] - 1068:8</p> <p><b>CIVIL</b> [1] - 1:5</p> <p><b>claim</b> [94] - 1009:1, 1009:20, 1009:23, 1015:17, 1015:23, 1017:14, 1049:13, 1051:24, 1055:22, 1057:16, 1140:7, 1155:17, 1155:18, 1188:22, 1191:25, 1193:15, 1194:14, 1194:16, 1194:23, 1195:1, 1195:4, 1195:17, 1196:2, 1196:23, 1197:12, 1197:14, 1197:15, 1197:21, 1198:1, 1198:4, 1222:11, 1222:21, 1222:24, 1223:18, 1223:20, 1223:25, 1224:2, 1224:18, 1224:20, 1227:12, 1227:20, 1228:23, 1228:25, 1229:5, 1229:6, 1231:20, 1231:21, 1231:23, 1232:1, 1234:19, 1235:1, 1235:2, 1235:3, 1235:24, 1236:9, 1237:3, 1237:20, 1237:22, 1237:23, 1238:9, 1238:23, 1245:5, 1245:6, 1245:8, 1245:14,</p>	<p>1246:7, 1246:11, 1246:20, 1247:14, 1247:21, 1247:25, 1251:8, 1251:14, 1251:17, 1252:4, 1252:18, 1252:22, 1253:7, 1253:10, 1253:11, 1254:11, 1254:12, 1254:23, 1255:1, 1255:3, 1255:7, 1256:8, 1256:14, 1256:15, 1270:9, 1270:18</p> <p><b>Claim</b> [50] - 1006:19, 1007:16, 1008:25, 1020:11, 1020:15, 1020:18, 1020:19, 1020:25, 1049:4, 1050:11, 1050:21, 1052:25, 1053:18, 1129:11, 1129:13, 1140:3, 1140:10, 1191:3, 1191:12, 1191:22, 1192:2, 1192:3, 1194:15, 1195:18, 1195:21, 1197:12, 1226:21, 1226:22, 1234:12, 1236:4, 1236:5, 1236:6, 1236:11, 1237:5, 1237:9, 1246:9, 1246:25, 1247:4, 1247:15, 1247:23, 1248:7, 1248:20, 1249:11, 1253:15, 1254:5, 1254:13, 1256:11</p> <p><b>claimed</b> [3] - 1008:7, 1073:7, 1198:11</p> <p><b>claims</b> [26] - 1057:16, 1057:22, 1155:8, 1155:12, 1155:20, 1191:3, 1191:7, 1192:5, 1192:14, 1195:14, 1222:16, 1222:18, 1229:8, 1234:5, 1234:9, 1234:23, 1236:3, 1241:11, 1246:9, 1246:19, 1247:12, 1247:19, 1252:23, 1265:2, 1269:11</p> <p><b>Claims</b> [3] - 1008:12, 1236:3, 1237:13</p> <p><b>clarify</b> [1] - 1014:4</p> <p><b>class</b> [4] - 1035:10, 1060:25, 1147:25, 1187:4</p> <p><b>classes</b> [1] - 1168:10</p> <p><b>classic</b> [2] - 1231:23,</p>	<p>1234:17</p> <p><b>clause</b> [1] - 1256:1</p> <p><b>cleaner</b> [1] - 1270:24</p> <p><b>clear</b> [21] - 1010:5, 1013:5, 1024:10, 1046:18, 1100:17, 1110:5, 1112:22, 1113:13, 1134:10, 1154:13, 1154:19, 1155:3, 1177:3, 1194:1, 1200:9, 1217:14, 1217:18, 1230:8, 1236:4, 1238:4, 1255:17</p> <p><b>clearance</b> [14] - 1097:15, 1097:18, 1097:25, 1132:14, 1133:5, 1133:6, 1133:9, 1133:15, 1133:24, 1133:25, 1134:4, 1138:12, 1143:20, 1152:1</p> <p><b>cleared</b> [4] - 1014:18, 1113:24, 1133:2, 1146:5</p> <p><b>clearly</b> [4] - 1045:23, 1057:7, 1240:24, 1253:7</p> <p><b>cleavage</b> [1] - 1078:10</p> <p><b>clerks</b> [2] - 1267:4, 1267:5</p> <p><b>client</b> [1] - 1232:5</p> <p><b>Clinic</b> [1] - 1138:10</p> <p><b>clinical</b> [40] - 1026:19, 1026:25, 1027:2, 1028:6, 1029:10, 1029:13, 1032:5, 1037:8, 1037:9, 1042:2, 1045:1, 1059:19, 1059:20, 1090:17, 1091:3, 1091:4, 1091:11, 1091:14, 1091:23, 1092:2, 1092:5, 1099:23, 1106:4, 1118:18, 1119:8, 1132:5, 1132:7, 1137:15, 1143:17, 1144:22, 1145:2, 1150:12, 1161:16, 1186:13, 1198:17, 1211:25, 1262:5, 1262:7, 1262:13, 1263:1</p> <p><b>Clinical</b> [4] - 1027:12, 1027:15, 1027:19, 1159:23</p> <p><b>clinically</b> [6] - 1086:6, 1089:10, 1090:11, 1091:25, 1153:22,</p>	<p>1155:25</p> <p><b>clinicaltrials.gov</b> [5] - 1121:21, 1182:15, 1182:19, 1261:19, 1261:20</p> <p><b>clinician</b> [5] - 1195:4, 1195:6, 1195:8, 1195:11, 1196:6</p> <p><b>clinics</b> [1] - 1219:20</p> <p><b>clock</b> [12] - 1068:11, 1084:25, 1085:5, 1164:15, 1164:23, 1165:1, 1168:3, 1168:16, 1175:12, 1202:25, 1203:18</p> <p><b>close</b> [8] - 1027:21, 1040:21, 1058:22, 1104:19, 1185:6, 1190:6, 1251:24, 1269:16</p> <p><b>closed</b> [1] - 1016:18</p> <p><b>closely</b> [2] - 1022:9, 1037:6</p> <p><b>closer</b> [4] - 1021:24, 1056:3, 1226:4, 1264:13</p> <p><b>closest</b> [1] - 1233:18</p> <p><b>closing</b> [5] - 1121:10, 1125:8, 1125:9, 1227:25, 1257:24</p> <p><b>closings</b> [2] - 1122:18, 1257:6</p> <p><b>CN</b> [2] - 1019:22, 1020:8</p> <p><b>CN019</b> [6] - 1021:11, 1021:16, 1022:5, 1022:11, 1022:13, 1023:4</p> <p><b>CN268</b> [5] - 1006:12, 1006:15, 1006:17, 1008:8, 1009:11</p> <p><b>coadminister</b> [3] - 1101:24, 1102:22, 1155:12</p> <p><b>coadministered</b> [2] - 1049:25, 1155:24</p> <p><b>coadministering</b> [2] - 1048:18, 1101:14</p> <p><b>coadministration</b> [10] - 1047:20, 1067:11, 1067:13, 1069:19, 1069:24, 1070:2, 1101:16, 1101:19, 1103:8, 1104:10</p> <p><b>coauthored</b> [2] - 1106:13, 1137:3</p> <p><b>coauthors</b> [1] - 1113:2</p> <p><b>COBLENTZ</b> [28] - 1005:16, 1127:18, 1128:24, 1136:12,</p>
---	--	---	---	---



<p>1137:10, 1139:22, 1142:17, 1142:19, 1147:15, 1147:16, 1150:15, 1150:16, 1151:3, 1151:8, 1155:2, 1155:6, 1156:11, 1156:13, 1157:1, 1157:5, 1157:10, 1157:14, 1158:11, 1158:19, 1159:16, 1159:19, 1161:22, 1162:1 <b>coeditor</b> [1] - 1027:14 <b>coeditor-in-chief</b> [1] - 1027:14 <b>cogent</b> [5] - 1086:5, 1089:10, 1090:10, 1090:17, 1091:24 <b>cognizant</b> [1] - 1157:13 <b>colleague</b> [1] - 1090:22 <b>colleagues</b> [2] - 1169:21, 1168:13 <b>collect</b> [1] - 1196:18 <b>collected</b> [2] - 1134:14, 1199:23 <b>collectively</b> [1] - 1241:22 <b>College</b> [4] - 1026:13, 1027:18, 1052:13, 1163:15 <b>college</b> [2] - 1063:16, 1063:17 <b>COLM</b> [1] - 1:19 <b>color</b> [1] - 1087:7 <b>column</b> [10] - 1022:17, 1063:9, 1149:24, 1151:10, 1160:10, 1161:9, 1235:18, 1235:19, 1235:20 <b>Column</b> [6] - 1035:6, 1036:1, 1038:24, 1242:14, 1253:2 <b>combination</b> [5] - 1051:10, 1054:14, 1056:22, 1057:1, 1184:12 <b>combinations</b> [3] - 1056:20, 1057:18, 1073:4 <b>combine</b> [4] - 1081:22, 1082:12, 1083:24, 1084:4 <b>combined</b> [2] - 1082:10, 1236:7 <b>combining</b> [1] - 1269:13 <b>comfortable</b> [3] - 1062:25, 1112:16,</p>	<p>1113:9 <b>coming</b> [2] - 1058:22, 1179:9 <b>comma</b> [1] - 1055:20 <b>commend</b> [2] - 1269:20, 1269:22 <b>comment</b> [6] - 1077:3, 1084:9, 1189:3, 1208:3, 1208:7, 1208:22 <b>comments</b> [1] - 1207:22 <b>commissioning</b> [1] - 1220:22 <b>commissions</b> [1] - 1220:19 <b>committee</b> [4] - 1181:7, 1207:16, 1207:23, 1218:23 <b>common</b> [9] - 1042:1, 1053:25, 1054:13, 1128:10, 1128:11, 1138:15, 1145:17, 1229:21, 1236:16 <b>commonly</b> [1] - 1233:12 <b>community</b> [4] - 1042:4, 1043:17, 1047:22, 1059:22 <b>companies</b> [5] - 1127:6, 1127:8, 1128:16, 1128:19, 1262:15 <b>company</b> [6] - 1113:23, 1113:25, 1126:24, 1127:11, 1145:12, 1262:5 <b>comparable</b> [1] - 1115:20 <b>compare</b> [2] - 1171:1, 1219:21 <b>compared</b> [5] - 1108:2, 1132:6, 1175:17, 1176:2, 1210:20 <b>comparing</b> [3] - 1040:7, 1044:16, 1210:19 <b>compelling</b> [3] - 1189:2, 1258:5, 1265:5 <b>competing</b> [5] - 1238:19, 1238:22, 1239:15, 1245:11, 1270:14 <b>compilation</b> [1] - 1063:9 <b>complete</b> [3] - 1081:22, 1098:8, 1271:12</p>	<p><b>completely</b> [1] - 1255:6 <b>completeness</b> [1] - 1007:18 <b>complicated</b> [1] - 1195:14 <b>components</b> [1] - 1098:7 <b>compose</b> [1] - 1188:8 <b>composition</b> [6] - 1009:2, 1258:13, 1258:14, 1259:7, 1259:8, 1259:9 <b>compositions</b> [1] - 1010:15 <b>compound</b> [8] - 1010:11, 1010:12, 1222:4, 1222:5, 1234:18, 1234:19, 1252:3, 1259:1 <b>compounds</b> [2] - 1107:22, 1108:9 <b>comprise</b> [2] - 1023:14, 1024:2 <b>comprises</b> [3] - 1192:3, 1196:14, 1236:6 <b>comprising</b> [1] - 1009:2 <b>concede</b> [2] - 1146:10, 1147:5 <b>conceding</b> [1] - 1063:16 <b>conceive</b> [2] - 1016:21, 1231:15 <b>concentration</b> [6] - 1035:17, 1044:22, 1134:12, 1142:4, 1142:10, 1189:22 <b>concentrations</b> [7] - 1041:21, 1044:14, 1044:17, 1045:9, 1046:14, 1046:16, 1142:8 <b>concern</b> [7] - 1045:17, 1117:20, 1118:13, 1118:17, 1132:7, 1133:20, 1140:25 <b>concerned</b> [2] - 1041:23, 1105:10 <b>concerning</b> [5] - 1011:21, 1035:7, 1039:1, 1129:11, 1158:21 <b>concerns</b> [2] - 1117:19, 1132:5 <b>conclude</b> [6] - 1024:22, 1112:3, 1112:5, 1248:7, 1252:22, 1255:12</p>	<p><b>concluded</b> [6] - 1019:7, 1058:15, 1112:10, 1248:15, 1255:19, 1272:2 <b>concludes</b> [3] - 1120:9, 1190:14, 1221:18 <b>conclusion</b> [7] - 1051:16, 1100:3, 1104:9, 1104:22, 1112:7, 1217:21, 1248:8 <b>conclusions</b> [1] - 1155:1 <b>concordance</b> [1] - 1236:8 <b>condition</b> [1] - 1190:25 <b>conditions</b> [3] - 1139:12, 1218:5, 1233:1 <b>conduct</b> [2] - 1096:10, 1144:21 <b>conducted</b> [10] - 1059:4, 1097:2, 1128:10, 1138:1, 1161:16, 1170:13, 1178:23, 1180:7, 1186:16, 1261:5 <b>confer</b> [7] - 1018:24, 1019:11, 1240:17, 1265:21, 1266:14, 1266:19, 1269:7 <b>conferred</b> [1] - 1257:14 <b>confess</b> [2] - 1205:10, 1239:17 <b>confident</b> [2] - 1125:19, 1180:3 <b>confirm</b> [1] - 1006:17 <b>confirmed</b> [3] - 1015:14, 1015:17, 1138:11 <b>conflicting</b> [1] - 1160:3 <b>conform</b> [2] - 1016:3, 1017:24 <b>conforming</b> [1] - 1187:11 <b>confront</b> [1] - 1087:12 <b>conjunction</b> [2] - 1231:2, 1255:9 <b>conjunctive</b> [1] - 1244:12 <b>connection</b> [1] - 1102:16 <b>connectivity</b> [1] - 1211:17 <b>CONNOLLY</b> [1] - 1:19 <b>consensus</b> [4] -</p>	<p>1043:5, 1058:22, 1173:19, 1174:3 <b>consequences</b> [4] - 1091:14, 1253:24, 1256:16, 1257:2 <b>consider</b> [9] - 1013:14, 1032:12, 1034:21, 1037:23, 1040:3, 1049:4, 1050:22, 1143:17, 1245:17 <b>consideration</b> [2] - 1041:24, 1245:16 <b>considerations</b> [1] - 1011:21 <b>considered</b> [9] - 1045:16, 1151:1, 1151:22, 1154:6, 1181:3, 1182:7, 1198:9, 1209:9, 1265:1 <b>considering</b> [2] - 1091:9, 1247:5 <b>consistent</b> [3] - 1088:21, 1234:8, 1241:2 <b>consolidated</b> [3] - 1166:6, 1166:19, 1202:24 <b>constantly</b> [1] - 1201:24 <b>constellation</b> [2] - 1102:18, 1104:16 <b>constitutes</b> [1] - 1015:21 <b>constitution</b> [1] - 1240:19 <b>constrained</b> [1] - 1165:2 <b>constructed</b> [1] - 1106:11 <b>construction</b> [17] - 1227:13, 1227:20, 1237:3, 1237:20, 1245:5, 1245:7, 1247:14, 1248:14, 1252:2, 1252:5, 1254:4, 1256:8, 1256:9, 1256:24, 1257:1, 1270:9, 1270:17 <b>constructions</b> [2] - 1246:19, 1270:15 <b>construe</b> [7] - 1226:19, 1228:13, 1237:16, 1238:1, 1238:9, 1238:23, 1256:13 <b>construed</b> [2] - 1233:13, 1252:23</p>
---	---	---	--	--

<p><b>construing</b> <sup>[1]</sup> - 1247:19</p> <p><b>consult</b> <sup>[1]</sup> - 1128:12</p> <p><b>Consulting</b> <sup>[2]</sup> - 1126:22, 1126:23</p> <p><b>consulting</b> <sup>[5]</sup> - 1127:2, 1212:22, 1213:6, 1213:13, 1213:16</p> <p><b>contact</b> <sup>[22]</sup> - 1227:6, 1229:17, 1229:22, 1230:9, 1231:6, 1231:7, 1241:1, 1241:9, 1241:24, 1242:8, 1245:9, 1246:24, 1247:3, 1248:7, 1248:15, 1248:18, 1248:20, 1249:24, 1252:19, 1255:8, 1255:13, 1255:25</p> <p><b>contacted</b> <sup>[1]</sup> - 1250:22</p> <p><b>contacting</b> <sup>[44]</sup> - 1113:20, 1229:20, 1229:24, 1230:2, 1230:5, 1231:3, 1231:4, 1231:9, 1231:13, 1231:15, 1231:18, 1232:6, 1232:10, 1232:17, 1240:4, 1240:9, 1240:12, 1240:22, 1240:23, 1241:5, 1241:8, 1241:13, 1242:3, 1242:16, 1242:17, 1242:23, 1243:1, 1243:3, 1243:7, 1243:16, 1243:17, 1243:23, 1244:1, 1248:11, 1249:21, 1250:25, 1251:2, 1251:9, 1255:6, 1255:20, 1255:22, 1256:21, 1256:23</p> <p><b>contain</b> <sup>[1]</sup> - 1034:8</p> <p><b>contained</b> <sup>[1]</sup> - 1155:11</p> <p><b>contemplating</b> <sup>[1]</sup> - 1266:1</p> <p><b>contention</b> <sup>[1]</sup> - 1062:16</p> <p><b>contents</b> <sup>[1]</sup> - 1030:14</p> <p><b>context</b> <sup>[12]</sup> - 1028:18, 1029:10, 1041:2, 1074:25, 1082:4, 1085:17, 1128:18, 1132:15, 1198:24, 1209:2, 1229:5,</p>	<p>1270:14</p> <p><b>continue</b> <sup>[1]</sup> - 1174:25</p> <p><b>continues</b> <sup>[1]</sup> - 1175:4</p> <p><b>contract</b> <sup>[2]</sup> - 1213:16, 1213:21</p> <p><b>Contraindications</b> <sup>[1]</sup> - 1068:23</p> <p><b>contraindications</b> <sup>[3]</sup> - 1049:22, 1068:25, 1069:8</p> <p><b>contribute</b> <sup>[1]</sup> - 1082:7</p> <p><b>contributes</b> <sup>[4]</sup> - 1051:8, 1132:4, 1133:23, 1143:19</p> <p><b>contributing</b> <sup>[4]</sup> - 1135:15, 1138:6, 1142:7, 1185:13</p> <p><b>contribution</b> <sup>[16]</sup> - 1081:16, 1081:19, 1081:21, 1081:24, 1082:3, 1131:24, 1132:3, 1132:9, 1132:13, 1132:16, 1134:4, 1134:6, 1134:7, 1134:10, 1141:23, 1141:25</p> <p><b>contributions</b> <sup>[3]</sup> - 1131:10, 1131:20, 1160:14</p> <p><b>contributor</b> <sup>[1]</sup> - 1131:25</p> <p><b>control</b> <sup>[3]</sup> - 1167:8, 1256:17, 1259:17</p> <p><b>controlled</b> <sup>[2]</sup> - 1141:16, 1179:21</p> <p><b>controls</b> <sup>[1]</sup> - 1141:19</p> <p><b>controversial</b> <sup>[1]</sup> - 1191:18</p> <p><b>conventional</b> <sup>[1]</sup> - 1174:1</p> <p><b>conversation</b> <sup>[2]</sup> - 1055:8, 1074:17</p> <p><b>conversations</b> <sup>[1]</sup> - 1074:22</p> <p><b>converted</b> <sup>[1]</sup> - 1135:9</p> <p><b>converting</b> <sup>[1]</sup> - 1192:10</p> <p><b>cookie</b> <sup>[3]</sup> - 1237:22, 1244:11, 1244:15</p> <p><b>copy</b> <sup>[2]</sup> - 1265:10, 1265:16</p> <p><b>corner</b> <sup>[3]</sup> - 1082:23, 1107:10, 1133:11</p> <p><b>corners</b> <sup>[2]</sup> - 1092:25, 1093:2</p> <p><b>corporation</b> <sup>[1]</sup> - 1113:6</p> <p><b>correct</b> <sup>[306]</sup> - 1007:2, 1009:8, 1010:8,</p>	<p>1013:12, 1013:23, 1023:14, 1051:14, 1052:23, 1053:2, 1053:3, 1053:10, 1053:17, 1053:20, 1053:21, 1053:25, 1054:4, 1058:20, 1059:13, 1059:14, 1059:18, 1059:24, 1059:25, 1060:10, 1060:11, 1060:15, 1060:16, 1061:1, 1061:5, 1061:12, 1061:21, 1061:22, 1062:2, 1062:10, 1062:19, 1063:1, 1063:4, 1063:14, 1063:15, 1063:18, 1063:20, 1064:25, 1066:11, 1066:12, 1066:14, 1066:15, 1066:20, 1067:7, 1067:8, 1067:12, 1067:19, 1068:3, 1069:21, 1070:4, 1070:10, 1070:15, 1070:18, 1070:23, 1070:24, 1071:5, 1071:14, 1072:9, 1072:10, 1072:23, 1073:1, 1073:10, 1073:23, 1074:7, 1074:8, 1074:13, 1075:3, 1075:8, 1075:9, 1075:12, 1075:13, 1075:15, 1075:16, 1075:19, 1075:20, 1075:22, 1076:1, 1076:2, 1076:5, 1076:6, 1076:9, 1076:10, 1076:14, 1076:22, 1077:2, 1077:6, 1077:10, 1077:18, 1077:24, 1078:6, 1078:9, 1078:12, 1078:16, 1078:17, 1078:19, 1078:23, 1079:2, 1079:6, 1079:9, 1079:15, 1079:16, 1080:18, 1080:21, 1080:24, 1080:25, 1081:2, 1081:3, 1081:6, 1081:7, 1081:9, 1081:13, 1081:14, 1081:17, 1082:1, 1082:8, 1083:7, 1083:9, 1083:14, 1083:16, 1083:21, 1084:1, 1084:6,</p>	<p>1084:16, 1084:21, 1085:18, 1085:19, 1085:23, 1085:24, 1086:2, 1086:3, 1086:6, 1089:10, 1089:12, 1089:18, 1090:7, 1090:19, 1090:20, 1090:25, 1091:14, 1091:18, 1091:25, 1092:4, 1092:10, 1092:11, 1092:14, 1092:21, 1093:1, 1093:7, 1093:8, 1093:10, 1093:13, 1093:17, 1093:18, 1094:1, 1095:5, 1096:23, 1097:3, 1097:19, 1097:25, 1098:1, 1098:5, 1098:12, 1098:13, 1098:15, 1098:21, 1098:22, 1098:23, 1098:24, 1099:1, 1099:25, 1100:1, 1100:8, 1100:9, 1100:12, 1100:19, 1100:24, 1101:4, 1101:14, 1101:19, 1102:11, 1102:17, 1102:23, 1102:24, 1103:10, 1103:14, 1103:15, 1103:17, 1103:18, 1105:6, 1105:15, 1106:16, 1106:17, 1107:7, 1108:3, 1108:10, 1108:13, 1108:14, 1108:17, 1108:21, 1109:1, 1109:3, 1109:5, 1109:9, 1109:12, 1109:13, 1109:16, 1109:22, 1109:23, 1110:6, 1110:7, 1110:9, 1112:1, 1113:17, 1113:20, 1113:25, 1114:6, 1114:7, 1115:24, 1118:14, 1124:7, 1127:25, 1128:6, 1131:7, 1133:17, 1135:3, 1140:8, 1140:9, 1142:24, 1143:2, 1143:3, 1143:6, 1143:11, 1144:24, 1145:6, 1145:10, 1145:16, 1145:19, 1146:1, 1146:7, 1146:16, 1146:23, 1147:12, 1148:10, 1148:11,</p>	<p>1148:15, 1148:21, 1148:24, 1149:1, 1149:6, 1151:20, 1151:24, 1154:17, 1155:10, 1155:17, 1155:22, 1156:4, 1156:9, 1156:18, 1156:22, 1157:17, 1157:18, 1157:20, 1157:23, 1159:10, 1159:11, 1159:13, 1164:5, 1171:17, 1191:5, 1191:9, 1199:5, 1199:16, 1199:20, 1199:25, 1200:8, 1200:18, 1200:19, 1201:2, 1204:10, 1210:1, 1210:17, 1210:18, 1210:24, 1211:4, 1211:14, 1211:20, 1212:9, 1212:10, 1212:13, 1212:23, 1213:8, 1213:12, 1213:15, 1213:24, 1214:3, 1220:20, 1221:4, 1228:8, 1241:25, 1242:4, 1243:9, 1250:14, 1270:18</p> <p><b>correctly</b> <sup>[1]</sup> - 1093:21</p> <p><b>correlation</b> <sup>[1]</sup> - 1150:23</p> <p><b>corresponds</b> <sup>[3]</sup> - 1007:3, 1007:15, 1008:12</p> <p><b>cost</b> <sup>[1]</sup> - 1118:7</p> <p><b>Counsel</b> <sup>[1]</sup> - 1086:12</p> <p><b>counsel</b> <sup>[3]</sup> - 1080:3, 1123:18, 1255:23</p> <p><b>count</b> <sup>[2]</sup> - 1121:7, 1193:5</p> <p><b>counted</b> <sup>[1]</sup> - 1216:14</p> <p><b>counter</b> <sup>[3]</sup> - 1139:9, 1139:11, 1139:17</p> <p><b>counting</b> <sup>[2]</sup> - 1122:4, 1122:18</p> <p><b>country</b> <sup>[5]</sup> - 1217:23, 1219:19, 1219:25, 1220:12, 1221:4</p> <p><b>couple</b> <sup>[9]</sup> - 1019:10, 1030:16, 1031:21, 1036:8, 1123:24, 1125:23, 1203:6, 1238:6, 1265:25</p> <p><b>course</b> <sup>[9]</sup> - 1057:9, 1057:10, 1111:20, 1164:12, 1171:5, 1193:2, 1234:22, 1252:20, 1260:16</p>
---	---	---	---	--

<p><b>COURT</b> [339] - 1:2, 1006:5, 1014:2, 1014:10, 1014:12, 1014:18, 1014:21, 1015:1, 1015:11, 1017:6, 1017:17, 1018:3, 1018:7, 1018:11, 1018:15, 1018:19, 1018:22, 1019:1, 1019:5, 1019:8, 1019:12, 1019:14, 1019:16, 1020:4, 1020:21, 1023:8, 1023:12, 1023:16, 1024:4, 1024:10, 1024:15, 1024:21, 1025:2, 1025:5, 1026:7, 1028:11, 1032:20, 1033:25, 1034:11, 1035:2, 1035:20, 1037:2, 1038:14, 1044:9, 1047:8, 1047:11, 1048:25, 1052:6, 1054:6, 1054:8, 1054:11, 1054:18, 1055:10, 1055:24, 1056:6, 1056:17, 1057:5, 1057:11, 1058:1, 1058:3, 1058:10, 1058:13, 1071:23, 1079:22, 1079:25, 1080:6, 1080:12, 1086:18, 1086:20, 1086:24, 1087:3, 1087:15, 1087:22, 1088:7, 1088:15, 1089:22, 1095:16, 1095:23, 1099:15, 1099:19, 1110:22, 1110:24, 1112:13, 1112:19, 1113:4, 1116:4, 1117:16, 1117:25, 1118:3, 1118:10, 1119:4, 1119:11, 1119:23, 1120:3, 1120:6, 1120:17, 1120:20, 1120:23, 1121:2, 1121:6, 1121:10, 1121:13, 1122:7, 1122:9, 1122:18, 1122:24, 1123:4, 1123:10, 1123:13, 1123:25, 1124:9, 1124:20, 1124:25, 1125:14, 1126:1, 1126:3, 1126:7, 1126:10, 1127:19, 1128:25, 1130:12,</p>	<p>1130:20, 1136:13, 1137:11, 1137:17, 1138:21, 1138:24, 1139:2, 1139:23, 1142:15, 1142:18, 1151:6, 1154:20, 1155:4, 1157:3, 1157:8, 1157:12, 1158:2, 1158:12, 1158:16, 1161:23, 1162:5, 1162:7, 1162:10, 1162:12, 1162:14, 1162:18, 1163:4, 1165:13, 1169:12, 1170:2, 1171:25, 1172:2, 1172:5, 1176:21, 1176:25, 1178:14, 1178:18, 1178:22, 1179:8, 1179:18, 1179:21, 1180:3, 1185:22, 1190:16, 1205:8, 1205:13, 1205:15, 1205:20, 1205:24, 1206:5, 1206:8, 1206:11, 1206:14, 1206:19, 1206:22, 1206:25, 1207:11, 1209:16, 1210:4, 1210:7, 1211:16, 1214:12, 1215:1, 1215:5, 1215:8, 1215:11, 1215:17, 1215:23, 1216:5, 1216:9, 1216:12, 1216:17, 1219:12, 1221:14, 1221:17, 1221:20, 1221:25, 1222:4, 1222:6, 1222:10, 1222:15, 1222:18, 1222:21, 1223:1, 1223:4, 1223:17, 1224:17, 1224:24, 1225:6, 1225:9, 1225:14, 1225:18, 1225:25, 1226:8, 1226:14, 1226:17, 1227:1, 1227:4, 1227:6, 1227:9, 1227:17, 1227:23, 1228:1, 1228:6, 1228:11, 1228:16, 1228:19, 1229:12, 1229:15, 1230:1, 1230:10, 1230:17, 1230:24, 1232:5, 1233:11, 1233:24, 1235:9, 1235:12, 1236:10, 1236:21, 1236:24, 1237:4,</p>	<p>1237:21, 1238:7, 1238:14, 1238:19, 1238:23, 1239:6, 1239:15, 1239:19, 1240:3, 1240:12, 1240:17, 1241:21, 1242:2, 1242:6, 1242:10, 1242:15, 1243:4, 1243:19, 1243:24, 1244:4, 1244:7, 1244:13, 1245:1, 1245:6, 1245:22, 1246:1, 1246:13, 1246:15, 1246:18, 1246:22, 1247:6, 1247:24, 1248:3, 1248:6, 1248:13, 1249:4, 1249:7, 1249:15, 1250:3, 1250:5, 1250:11, 1250:14, 1250:18, 1250:23, 1253:13, 1253:15, 1253:20, 1253:22, 1253:25, 1254:4, 1254:8, 1254:15, 1254:25, 1257:7, 1257:24, 1258:19, 1258:23, 1259:4, 1259:24, 1260:8, 1260:20, 1261:1, 1261:6, 1261:15, 1261:18, 1261:22, 1261:24, 1262:9, 1262:17, 1262:22, 1263:7, 1263:21, 1264:4, 1264:8, 1264:11, 1264:23, 1265:3, 1265:15, 1265:22, 1266:10, 1266:13, 1266:15, 1266:20, 1267:4, 1267:8, 1267:17, 1268:6, 1268:10, 1268:15, 1269:2, 1269:6, 1270:12, 1271:2, 1271:6, 1271:13, 1271:20</p> <p><b>court</b> [10] - 1058:18, 1065:3, 1089:2, 1113:1, 1137:17, 1182:16, 1233:13, 1264:24, 1269:24, 1271:8</p> <p><b>Court</b> [30] - 1014:15, 1024:13, 1024:14, 1028:14, 1030:9, 1035:21, 1048:11, 1055:25, 1057:15, 1062:1, 1074:23, 1079:21, 1086:16,</p>	<p>1123:21, 1124:18, 1125:23, 1138:17, 1139:4, 1163:6, 1181:7, 1216:15, 1229:11, 1245:23, 1251:25, 1257:5, 1257:22, 1261:12, 1265:21, 1270:22, 1272:7</p> <p><b>courtesy</b> [1] - 1113:1</p> <p><b>Courtroom</b> [1] - 1006:4</p> <p><b>courtroom</b> [10] - 1015:2, 1087:3, 1087:19, 1088:9, 1109:24, 1164:4, 1174:9, 1184:7, 1188:18, 1217:3</p> <p><b>courts</b> [1] - 1057:6</p> <p><b>cover</b> [6] - 1165:19, 1177:21, 1177:24, 1188:1, 1222:8, 1245:14</p> <p><b>covered</b> [4] - 1224:13, 1237:5, 1238:3, 1254:10</p> <p><b>COZEN</b> [1] - 1005:15</p> <p><b>crack</b> [1] - 1271:1</p> <p><b>cream</b> [3] - 1138:22, 1154:14, 1185:11</p> <p><b>create</b> [1] - 1065:8</p> <p><b>creative</b> [4] - 1182:3, 1182:12, 1269:3, 1269:19</p> <p><b>credibility</b> [1] - 1223:7</p> <p><b>credible</b> [3] - 1258:2, 1264:15, 1264:19</p> <p><b>CROSS</b> [5] - 1006:7, 1052:7, 1142:16, 1190:17, 1220:16</p> <p><b>cross</b> [14] - 1015:13, 1018:4, 1055:5, 1056:15, 1080:1, 1123:14, 1123:15, 1142:15, 1158:4, 1176:4, 1190:16, 1205:21, 1206:3, 1207:7</p> <p><b>CROSS-EXAMINATION</b> [4] - 1006:7, 1052:7, 1142:16, 1190:17</p> <p><b>cross-examination</b> [4] - 1015:13, 1018:4, 1055:5, 1080:1</p> <p><b>cross-examine</b> [1] - 1056:15</p> <p><b>cross-react</b> [1] - 1176:4</p> <p><b>crossover</b> [1] -</p>	<p>1172:17</p> <p><b>crowded</b> [1] - 1015:2</p> <p><b>CRR</b> [2] - 2:1, 1272:7</p> <p><b>culled</b> [1] - 1131:9</p> <p><b>cures</b> [1] - 1118:21</p> <p><b>curiosity</b> [2] - 1155:1, 1220:1</p> <p><b>curious</b> [3] - 1216:12, 1216:19, 1216:21</p> <p><b>current</b> [2] - 1025:20, 1062:9</p> <p><b>Current</b> [1] - 1061:20</p> <p><b>curriculum</b> [2] - 1127:15, 1169:7</p> <p><b>curve</b> [30] - 1044:22, 1046:11, 1168:23, 1170:9, 1170:12, 1171:2, 1171:8, 1171:11, 1172:10, 1172:15, 1173:10, 1173:18, 1173:21, 1177:15, 1178:5, 1178:15, 1180:22, 1183:5, 1183:17, 1199:15, 1199:16, 1201:5, 1201:10, 1201:23, 1202:7, 1202:10, 1202:11, 1203:12, 1203:13</p> <p><b>curves</b> [6] - 1168:18, 1168:19, 1170:13, 1172:13, 1173:22, 1178:15</p> <p><b>cut</b> [3] - 1123:12, 1183:12, 1186:3</p> <p><b>CV</b> [4] - 1026:3, 1216:1, 1216:18, 1219:9</p> <p><b>CVs</b> [1] - 1216:2</p> <p><b>cycle</b> [11] - 1166:5, 1170:14, 1170:17, 1178:24, 1190:4, 1191:5, 1191:9, 1192:17, 1196:13, 1197:10, 1204:17</p> <p><b>CYP</b> [43] - 1031:5, 1031:10, 1031:19, 1031:20, 1031:23, 1032:25, 1033:6, 1040:11, 1041:11, 1042:9, 1051:9, 1060:25, 1064:22, 1065:5, 1065:8, 1068:5, 1069:13, 1069:17, 1073:22, 1075:11, 1081:1, 1082:6, 1096:13, 1103:7, 1114:24, 1128:9, 1130:8, 1131:11, 1131:20,</p>
--	---	--	--	---

<p>1132:3, 1133:9, 1133:12, 1133:14, 1134:18, 1146:6, 1148:9, 1148:14, 1150:5, 1160:13, 1161:2</p> <p><b>CYP1A</b> [1] - 1115:22 <b>CYP1A1</b> [1] - 1160:12 <b>CYP1A2</b> [61] - 1028:25, 1031:16, 1036:8, 1039:4, 1040:23, 1043:3, 1043:6, 1048:2, 1049:8, 1049:19, 1053:1, 1060:1, 1060:3, 1060:24, 1062:19, 1063:3, 1066:8, 1066:14, 1066:20, 1067:11, 1067:25, 1069:25, 1073:25, 1092:14, 1092:19, 1093:6, 1093:10, 1093:12, 1100:3, 1100:6, 1100:8, 1100:11, 1100:12, 1100:21, 1100:23, 1101:10, 1101:12, 1101:23, 1102:10, 1102:22, 1103:8, 1114:21, 1115:22, 1129:12, 1139:15, 1147:9, 1148:10, 1148:24, 1149:1, 1149:2, 1149:5, 1155:10, 1155:16, 1156:3, 1156:8, 1160:12, 1161:2, 1161:11, 1161:14, 1161:18, 1188:23</p> <p><b>CYP2A6</b> [1] - 1115:23 <b>CYP2C19</b> [3] - 1147:9, 1160:14, 1161:4 <b>CYP2C9</b> [4] - 1115:23, 1147:9, 1160:12, 1161:4 <b>CYP2D6</b> [5] - 1115:23, 1147:9, 1148:3, 1160:12, 1161:4 <b>CYP2E1</b> [1] - 1139:15 <b>CYP3A</b> [5] - 1029:3, 1032:1, 1032:2, 1046:12, 1048:3 <b>CYP3A4</b> [54] - 1030:18, 1039:8, 1040:24, 1043:11, 1043:15, 1051:7, 1051:15, 1051:17, 1051:20, 1053:18, 1053:24, 1054:3,</p>	<p>1055:6, 1060:12, 1060:15, 1067:7, 1070:9, 1093:11, 1099:23, 1102:5, 1103:22, 1103:23, 1104:23, 1105:11, 1112:7, 1116:10, 1116:19, 1136:23, 1137:16, 1138:3, 1138:6, 1139:15, 1140:12, 1140:15, 1140:22, 1140:23, 1140:25, 1141:7, 1141:23, 1141:24, 1142:2, 1146:6, 1146:15, 1146:21, 1147:1, 1147:9, 1147:10, 1148:2, 1148:10, 1148:20, 1148:25, 1155:22, 1156:8, 1189:9 <b>CYP3A4/5</b> [3] - 1161:2, 1161:14, 1161:19 <b>CYP450</b> [1] - 1031:8 <b>CYPs</b> [2] - 1032:3, 1083:21 <b>cytochrome</b> [20] - 1031:5, 1031:10, 1060:25, 1073:9, 1114:19, 1131:3, 1131:16, 1132:14, 1132:16, 1133:20, 1133:22, 1136:20, 1136:22, 1141:17, 1142:6, 1143:18, 1143:19, 1145:24, 1147:21, 1160:12 <b>Czeisler</b> [20] - 1120:22, 1123:9, 1162:20, 1162:25, 1163:7, 1163:8, 1169:15, 1170:7, 1172:9, 1190:19, 1190:22, 1205:8, 1207:15, 1208:7, 1209:8, 1210:4, 1210:12, 1212:7, 1217:4, 1218:22 <b>CZEISLER</b> [1] - 1162:21</p>	<p>1173:7, 1175:11, 1183:4, 1183:20, 1183:23, 1196:10, 1196:16, 1196:25, 1197:7, 1203:7, 1227:15, 1239:24 <b>DANIEL</b> [1] - 1005:10 <b>dark</b> [1] - 1203:9 <b>darkness</b> [4] - 1170:23, 1199:25, 1202:5, 1203:3 <b>dash</b> [1] - 1149:18 <b>data</b> [42] - 1022:5, 1022:11, 1033:12, 1039:11, 1045:1, 1046:20, 1046:21, 1050:15, 1066:23, 1073:9, 1092:9, 1092:12, 1093:5, 1093:9, 1093:14, 1093:18, 1097:22, 1098:5, 1098:7, 1098:15, 1098:20, 1100:24, 1100:25, 1101:3, 1101:18, 1101:25, 1106:6, 1106:7, 1106:10, 1106:11, 1112:3, 1134:8, 1152:21, 1152:24, 1153:4, 1153:7, 1164:22, 1166:24, 1199:23, 1217:14, 1217:25 <b>Data</b> [1] - 1094:6 <b>date</b> [26] - 1017:12, 1042:11, 1050:17, 1053:7, 1059:3, 1059:9, 1059:18, 1073:7, 1092:3, 1092:8, 1092:17, 1093:7, 1093:17, 1097:1, 1097:21, 1098:2, 1098:10, 1100:6, 1101:7, 1106:16, 1173:24, 1174:3, 1199:3, 1261:9, 1261:18, 1270:1 <b>dates</b> [2] - 1266:12, 1269:10 <b>daughter</b> [1] - 1074:19 <b>David</b> [1] - 1025:13 <b>days</b> [4] - 1093:23, 1164:5, 1190:23, 1258:8 <b>daytime</b> [3] - 1167:5, 1168:12, 1183:25 <b>DDI</b> [4] - 1152:5, 1152:20, 1153:4, 1153:9</p>	<p><b>DDIs</b> [4] - 1151:13, 1151:19, 1151:23, 1152:4 <b>DDX-6.1</b> [1] - 1025:18 <b>DDX-6.10</b> [2] - 1032:23, 1079:19 <b>DDX-6.12</b> [2] - 1027:10, 1040:25 <b>DDX-6.13</b> [1] - 1042:8 <b>DDX-6.14</b> [1] - 1043:18 <b>DDX-6.15</b> [1] - 1045:24 <b>DDX-6.16</b> [1] - 1046:4 <b>DDX-6.17</b> [1] - 1047:6 <b>DDX-6.18</b> [1] - 1047:23 <b>DDX-6.19</b> [1] - 1048:10 <b>DDX-6.2</b> [1] - 1027:5 <b>DDX-6.21</b> [1] - 1049:3 <b>DDX-6.23</b> [1] - 1050:20 <b>DDX-6.3</b> [1] - 1027:24 <b>DDX-6.4</b> [1] - 1028:13 <b>DDX-6.5</b> [1] - 1028:21 <b>DDX-6.6</b> [1] - 1029:5 <b>DDX-6.7</b> [1] - 1030:5 <b>DDX-6.8</b> [1] - 1031:7 <b>DDX-6.9</b> [1] - 1031:18 <b>deal</b> [2] - 1222:1, 1228:11 <b>dealing</b> [5] - 1119:17, 1119:21, 1121:19, 1182:1 <b>deals</b> [2] - 1129:14, 1184:16 <b>death</b> [2] - 1119:7, 1119:10 <b>debate</b> [4] - 1016:16, 1088:21, 1244:22, 1246:23 <b>debating</b> [1] - 1181:23 <b>debilitating</b> [1] - 1186:18 <b>decade</b> [1] - 1212:24 <b>decades</b> [2] - 1043:14, 1186:20 <b>December</b> [1] - 1265:24 <b>decent</b> [1] - 1021:21 <b>decide</b> [5] - 1098:4, 1101:23, 1224:4, 1231:12, 1268:10 <b>decides</b> [1] - 1210:8 <b>decision</b> [7] - 1014:23, 1096:3, 1098:4, 1098:11, 1182:2, 1270:11, 1270:12</p>	<p><b>decisions</b> [1] - 1257:11 <b>deck</b> [2] - 1052:20, 1199:8 <b>declaration</b> [2] - 1160:3, 1269:12 <b>decrease</b> [5] - 1046:13, 1046:15, 1048:2, 1051:9, 1152:6 <b>decreased</b> [1] - 1047:3 <b>decreases</b> [1] - 1041:12 <b>deduced</b> [1] - 1069:9 <b>deep</b> [1] - 1234:23 <b>Defendant</b> [1] - 1:9 <b>defendant</b> [3] - 1124:11, 1125:5, 1265:18 <b>defendant's</b> [1] - 1270:18 <b>defendants</b> [19] - 1023:19, 1024:25, 1026:4, 1028:5, 1032:17, 1034:24, 1036:24, 1038:10, 1042:22, 1044:6, 1073:3, 1121:22, 1121:25, 1122:3, 1215:18, 1236:22, 1255:2, 1269:13, 1270:7 <b>defendants'</b> [3] - 1057:18, 1080:11, 1120:10 <b>defined</b> [5] - 1055:25, 1231:24, 1233:10, 1243:11, 1243:12 <b>defines</b> [1] - 1241:24 <b>defining</b> [1] - 1190:25 <b>definitely</b> [1] - 1254:19 <b>definition</b> [1] - 1251:7 <b>definitive</b> [1] - 1145:7 <b>degree</b> [3] - 1090:15, 1090:16, 1163:18 <b>DEIRDE</b> [1] - 1005:4 <b>DELAWARE</b> [1] - 1:3 <b>Delaware</b> [1] - 1:15 <b>delay</b> [5] - 1178:5, 1180:22, 1183:4, 1183:16, 1204:8 <b>delayed</b> [5] - 1168:6, 1184:1, 1201:12, 1203:15, 1220:10 <b>delaying</b> [2] - 1200:17, 1201:18 <b>delays</b> [3] - 1172:16, 1172:19, 1267:18</p>
	<p><b>D</b></p>			
	<p><b>daily</b> [25] - 1165:4, 1165:22, 1166:17, 1166:18, 1167:7, 1167:10, 1167:12, 1167:18, 1167:22, 1168:4, 1168:9, 1168:11, 1168:15,</p>			



<b>deliberately</b> [1] - 1157:24	1073:9, 1103:3, 1240:25	1021:9, 1021:13, 1167:15	1235:3, 1235:25, 1237:19	<b>discussions</b> [1] - 1232:7
<b>delineate</b> [1] - 1085:25	<b>description</b> [12] - 1192:6, 1232:8, 1235:6, 1235:15, 1236:1, 1236:9, 1237:18, 1238:5, 1242:3, 1242:22, 1244:21, 1244:25	<b>different</b> [45] - 1016:10, 1020:10, 1020:19, 1020:22, 1020:23, 1020:24, 1021:2, 1021:3, 1021:11, 1021:12, 1041:10, 1041:17, 1060:23, 1074:15, 1074:22, 1079:2, 1079:3, 1081:4, 1082:9, 1083:4, 1087:18, 1088:6, 1095:14, 1108:25, 1111:18, 1113:7, 1115:21, 1134:4, 1134:10, 1138:18, 1139:6, 1148:9, 1157:21, 1172:13, 1187:18, 1187:20, 1190:4, 1202:21, 1230:20, 1231:4, 1231:15, 1243:11, 1244:13, 1256:22, 1263:15	<b>directness</b> [1] - 1258:3 <b>disability</b> [1] - 1186:21 <b>disagree</b> [7] - 1016:7, 1129:20, 1189:18, 1189:19, 1217:11, 1217:13, 1229:20 <b>disbelieve</b> [1] - 1016:12 <b>disclose</b> [8] - 1034:18, 1035:7, 1036:3, 1038:20, 1038:25, 1039:7, 1049:18, 1051:13 <b>disclosed</b> [9] - 1020:11, 1021:10, 1021:16, 1022:11, 1072:9, 1092:23, 1092:24, 1252:24, 1263:25 <b>discloses</b> [5] - 1010:14, 1049:19, 1131:24, 1189:19, 1189:20 <b>disclosure</b> [2] - 1017:9, 1190:12 <b>disclosures</b> [1] - 1116:16 <b>discontinue</b> [2] - 1049:9, 1051:1 <b>discount</b> [1] - 1264:18 <b>discoveries</b> [1] - 1164:12 <b>discovering</b> [1] - 1164:13 <b>discretion</b> [1] - 1249:1 <b>discretionary</b> [1] - 1226:7 <b>discuss</b> [5] - 1028:14, 1028:16, 1149:14, 1157:6, 1157:10 <b>discussed</b> [12] - 1018:25, 1039:12, 1083:9, 1083:12, 1109:11, 1135:4, 1149:13, 1174:10, 1175:6, 1184:7, 1210:2, 1218:20 <b>discussion</b> [13] - 1014:24, 1019:6, 1054:9, 1058:14, 1123:17, 1152:8, 1157:7, 1168:17, 1182:18, 1267:3, 1268:14, 1268:21, 1269:5 <b>Discussion</b> [2] - 1152:16, 1211:18	<b>diseases</b> [1] - 1109:25 <b>disjunctive</b> [1] - 1244:12 <b>dismissal</b> [1] - 1271:16 <b>disorder</b> [24] - 1164:17, 1167:9, 1167:21, 1167:22, 1168:6, 1168:14, 1179:19, 1179:20, 1184:2, 1186:11, 1186:18, 1192:1, 1192:2, 1192:9, 1192:15, 1194:17, 1196:8, 1200:1, 1203:16, 1220:7, 1220:10, 1222:13, 1222:23, 1223:6 <b>Disorder</b> [1] - 1192:4 <b>disorders</b> [5] - 1037:8, 1062:6, 1163:2, 1164:2, 1167:20 <b>Disorders</b> [1] - 1163:9 <b>Disposition</b> [1] - 1039:21 <b>dispositive</b> [2] - 1247:8, 1248:23 <b>dispute</b> [6] - 1077:12, 1227:15, 1229:9, 1238:14, 1238:16, 1241:3 <b>disputed</b> [1] - 1238:25 <b>disputes</b> [2] - 1124:19, 1124:23 <b>disqualification</b> [1] - 1012:10 <b>dissolves</b> [1] - 1030:13 <b>distinction</b> [1] - 1105:23 <b>distinguishes</b> [1] - 1244:15 <b>DISTRICT</b> [2] - 1:2, 1:3 <b>District</b> [1] - 1272:7 <b>disturbing</b> [1] - 1171:1 <b>Division</b> [2] - 1163:9, 1163:12 <b>divisions</b> [1] - 1076:7 <b>DNA</b> [1] - 1065:17 <b>docket</b> [2] - 1270:25, 1271:18 <b>Doctor</b> [28] - 1012:16, 1028:21, 1029:5, 1032:23, 1034:14, 1038:7, 1038:19, 1039:19, 1044:13, 1045:24, 1046:9,
<b>demonstrate</b> [14] - 1194:16, 1194:18, 1194:19, 1195:2, 1195:5, 1195:9, 1196:1, 1196:6, 1196:19, 1196:22, 1196:23, 1197:18, 1223:9	<b>Design</b> [1] - 1094:6 <b>design</b> [1] - 1182:12 <b>designed</b> [1] - 1253:7 <b>desirable</b> [2] - 1152:19, 1153:3 <b>desire</b> [1] - 1184:22 <b>desired</b> [3] - 1174:5, 1183:6, 1203:20 <b>despite</b> [4] - 1105:2, 1105:8, 1135:17 <b>detail</b> [1] - 1263:2 <b>detailed</b> [1] - 1069:8 <b>detect</b> [1] - 1116:20 <b>detected</b> [1] - 1023:2 <b>determine</b> [8] - 1057:2, 1077:16, 1080:17, 1084:20, 1085:16, 1145:5, 1145:9, 1159:3 <b>determined</b> [4] - 1022:6, 1131:11, 1131:21, 1132:1 <b>determining</b> [3] - 1022:4, 1143:9, 1143:24 <b>develop</b> [1] - 1211:7 <b>developed</b> [3] - 1013:17, 1072:11, 1173:23 <b>developing</b> [2] - 1209:23, 1260:17 <b>development</b> [13] - 1029:15, 1029:25, 1030:1, 1033:19, 1033:22, 1093:24, 1105:15, 1105:21, 1106:1, 1127:1, 1128:18, 1150:12, 1262:11 <b>Development</b> [1] - 1027:12 <b>diabetes</b> [1] - 1185:13 <b>diagnosis</b> [1] - 1164:1 <b>diagram</b> [1] - 1204:7 <b>dictionary</b> [1] - 1251:6 <b>differ</b> [1] - 1174:16 <b>difference</b> [6] - 1063:17, 1074:17, 1090:13, 1094:22, 1158:18, 1242:21 <b>differences</b> [3] -	<b>differentiated</b> [1] - 1052:22 <b>differently</b> [1] - 1231:10 <b>differing</b> [1] - 1173:16 <b>difficult</b> [3] - 1166:20, 1166:23, 1203:5 <b>difficulty</b> [2] - 1165:10, 1229:1 <b>dihydrobenzofuran</b> [2] - 1108:10, 1156:17 <b>dim</b> [1] - 1170:23 <b>DIRECT</b> [4] - 1025:8, 1126:14, 1162:23, 1216:24 <b>direct</b> [24] - 1015:7, 1053:20, 1055:5, 1063:13, 1063:23, 1064:18, 1064:25, 1066:10, 1067:10, 1067:17, 1080:16, 1093:18, 1093:19, 1095:4, 1105:12, 1109:22, 1123:5, 1154:12, 1156:24, 1163:11, 1199:1, 1202:13, 1229:6, 1264:22 <b>direction</b> [1] - 1183:9 <b>directions</b> [1] - 1041:10 <b>directly</b> [6] - 1072:19, 1077:20, 1234:15,		

<p>1047:13, 1050:20, 1058:20, 1164:4, 1165:8, 1165:21, 1168:18, 1180:6, 1184:15, 1184:21, 1186:4, 1188:1, 1192:22, 1194:21, 1195:13, 1208:5, 1214:15</p> <p><b>doctor</b> [8] - 1041:3, 1052:19, 1059:2, 1165:16, 1183:10, 1188:4, 1203:24, 1215:23</p> <p><b>doctors</b> [2] - 1187:19, 1216:9</p> <p><b>Document</b> [1] - 1039:14</p> <p><b>document</b> [30] - 1026:2, 1034:16, 1034:18, 1034:21, 1036:12, 1036:18, 1037:21, 1038:4, 1038:7, 1054:16, 1054:20, 1073:15, 1082:17, 1093:3, 1094:4, 1094:18, 1095:5, 1095:13, 1095:15, 1095:19, 1099:5, 1099:10, 1114:3, 1114:8, 1114:17, 1160:20, 1160:24, 1184:8, 1209:8</p> <p><b>documents</b> [7] - 1009:17, 1010:7, 1052:22, 1072:21, 1073:1, 1073:12, 1122:1</p> <p><b>domain</b> [3] - 1092:6, 1156:5, 1156:10</p> <p><b>domestic</b> [1] - 1016:11</p> <p><b>dominant</b> [1] - 1032:3</p> <p><b>dominated</b> [1] - 1132:6</p> <p><b>done</b> [20] - 1011:7, 1018:4, 1018:5, 1018:7, 1033:8, 1033:10, 1065:7, 1065:11, 1104:24, 1106:3, 1122:17, 1125:13, 1126:6, 1128:15, 1128:18, 1131:13, 1170:23, 1241:22, 1259:20, 1265:24</p> <p><b>donut</b> [1] - 1112:23</p> <p><b>dosage</b> [11] - 1091:5, 1091:11, 1091:12,</p>	<p>1096:22, 1098:5, 1098:11, 1176:21, 1180:16, 1202:8, 1204:6, 1221:8</p> <p><b>dose</b> [17] - 1111:15, 1119:20, 1138:11, 1175:8, 1175:10, 1175:17, 1176:2, 1176:18, 1177:1, 1178:4, 1178:11, 1178:12, 1181:2, 1181:3, 1181:4, 1190:3, 1218:14</p> <p><b>doses</b> [1] - 1173:18</p> <p><b>dosing</b> [1] - 1180:10</p> <p><b>Dosing</b> [1] - 1094:6</p> <p><b>dot</b> [1] - 1030:11</p> <p><b>doubt</b> [3] - 1141:5, 1213:22, 1255:18</p> <p><b>dough</b> [2] - 1244:11, 1244:15</p> <p><b>down</b> [31] - 1006:21, 1008:15, 1014:12, 1023:17, 1030:12, 1031:14, 1035:23, 1037:10, 1046:14, 1056:21, 1056:25, 1064:2, 1076:8, 1099:7, 1106:22, 1111:12, 1119:24, 1123:12, 1133:7, 1150:15, 1186:3, 1208:3, 1214:5, 1214:8, 1215:12, 1221:14, 1229:9, 1231:25, 1237:25, 1247:19</p> <p><b>downregulated</b> [1] - 1093:16</p> <p><b>Dr</b> [142] - 1006:6, 1006:9, 1013:25, 1015:7, 1015:14, 1016:11, 1019:17, 1019:20, 1020:7, 1023:19, 1023:23, 1025:10, 1025:15, 1025:20, 1025:23, 1026:12, 1026:21, 1027:5, 1027:24, 1028:6, 1028:13, 1030:5, 1037:5, 1038:9, 1039:20, 1039:24, 1044:1, 1052:9, 1064:4, 1068:7, 1080:14, 1089:7, 1106:22, 1114:5, 1115:11, 1116:8, 1120:19, 1120:22, 1123:8, 1126:16, 1126:19,</p>	<p>1127:22, 1128:4, 1128:22, 1129:2, 1129:8, 1129:16, 1129:25, 1130:17, 1130:24, 1132:23, 1134:25, 1137:4, 1137:14, 1137:23, 1138:10, 1138:24, 1139:4, 1140:2, 1140:20, 1142:20, 1142:23, 1143:4, 1145:21, 1146:12, 1147:7, 1147:18, 1148:6, 1148:7, 1148:12, 1149:12, 1150:19, 1151:18, 1155:7, 1156:1, 1159:20, 1162:20, 1162:25, 1163:7, 1163:8, 1167:11, 1167:17, 1168:7, 1169:15, 1169:21, 1170:7, 1170:20, 1171:7, 1171:10, 1171:14, 1171:15, 1172:9, 1172:10, 1173:17, 1173:20, 1174:9, 1174:13, 1175:3, 1175:14, 1181:13, 1181:16, 1181:22, 1183:21, 1189:1, 1189:2, 1190:19, 1190:22, 1199:21, 1199:22, 1204:20, 1204:21, 1205:8, 1205:21, 1206:4, 1207:7, 1207:15, 1208:12, 1209:8, 1210:4, 1210:12, 1211:5, 1212:7, 1215:19, 1215:21, 1216:1, 1216:8, 1217:1, 1217:3, 1217:4, 1217:24, 1218:21, 1218:22, 1219:9, 1219:15, 1220:18, 1228:9, 1258:1, 1261:9</p> <p><b>draft</b> [6] - 1094:10, 1094:15, 1094:19, 1094:20, 1159:12, 1270:4</p> <p><b>drawing</b> [1] - 1154:25</p> <p><b>dream</b> [1] - 1177:25</p> <p><b>drift</b> [1] - 1183:20</p> <p><b>drifting</b> [1] - 1202:5</p> <p><b>drive</b> [4] - 1185:2, 1203:1, 1203:12, 1203:17</p>	<p><b>drop</b> [1] - 1268:7</p> <p><b>dropped</b> [2] - 1193:12, 1271:17</p> <p><b>Drs</b> [1] - 1188:18</p> <p><b>Drug</b> [5] - 1039:21, 1062:4, 1094:5, 1159:23</p> <p><b>drug</b> [225] - 1013:12, 1013:18, 1013:19, 1028:7, 1028:19, 1029:11, 1029:14, 1030:15, 1030:24, 1031:3, 1031:6, 1031:19, 1031:22, 1031:24, 1032:25, 1033:16, 1033:17, 1033:19, 1033:22, 1036:7, 1037:6, 1041:1, 1041:3, 1041:6, 1041:8, 1041:11, 1041:12, 1041:13, 1041:16, 1041:20, 1041:21, 1041:22, 1041:23, 1041:25, 1045:18, 1045:25, 1046:3, 1046:5, 1046:17, 1047:16, 1047:17, 1047:18, 1047:24, 1051:11, 1051:23, 1057:16, 1057:22, 1069:19, 1076:17, 1077:16, 1077:17, 1077:20, 1077:22, 1078:23, 1079:2, 1079:9, 1079:11, 1079:13, 1080:17, 1081:1, 1084:18, 1091:5, 1091:9, 1091:11, 1091:12, 1091:17, 1091:22, 1093:15, 1093:24, 1096:11, 1097:6, 1097:8, 1097:13, 1099:23, 1100:21, 1103:9, 1106:6, 1108:20, 1109:16, 1116:14, 1117:1, 1117:10, 1118:20, 1118:21, 1118:24, 1119:1, 1119:17, 1119:21, 1126:25, 1127:1, 1127:3, 1127:9, 1128:18, 1128:22, 1131:17, 1132:7, 1132:10, 1133:7, 1133:21, 1134:11, 1134:13, 1134:15, 1134:19, 1135:1, 1135:8,</p>	<p>1135:10, 1135:11, 1135:12, 1135:14, 1135:18, 1135:22, 1135:23, 1136:17, 1137:15, 1141:14, 1141:23, 1142:3, 1142:5, 1142:8, 1143:9, 1143:11, 1143:17, 1143:20, 1143:24, 1144:1, 1144:14, 1144:22, 1144:23, 1145:5, 1145:8, 1145:10, 1145:13, 1145:15, 1145:24, 1148:8, 1148:13, 1148:17, 1150:4, 1150:10, 1150:11, 1150:12, 1153:22, 1154:9, 1155:9, 1155:13, 1155:16, 1155:21, 1158:23, 1158:25, 1159:1, 1159:2, 1159:3, 1177:4, 1178:19, 1179:14, 1179:25, 1181:21, 1182:5, 1183:15, 1188:16, 1188:23, 1189:9, 1211:3, 1259:12, 1262:6</p> <p><b>Drug-Drug</b> [1] - 1159:23</p> <p><b>drug-drug</b> [52] - 1041:1, 1041:3, 1041:23, 1045:25, 1046:5, 1047:16, 1047:24, 1051:23, 1057:16, 1057:22, 1077:17, 1091:9, 1091:17, 1091:22, 1096:11, 1108:20, 1109:16, 1116:14, 1117:1, 1117:10, 1127:1, 1127:3, 1127:9, 1128:22, 1134:19, 1135:1, 1135:8, 1135:23, 1143:9, 1143:11, 1143:24, 1144:1, 1144:14, 1144:22, 1144:23, 1145:5, 1145:8, 1145:10, 1145:13, 1145:15, 1145:24, 1148:8, 1148:13, 1155:9, 1155:13, 1155:16, 1155:21, 1158:25, 1159:1, 1188:16, 1188:23, 1189:9</p> <p><b>drug-metabolizing</b> [1] - 1133:7</p>
--	---	---	---	---

<p><b>drugs</b> [65] - 1026:22, 1027:1, 1029:17, 1029:23, 1032:4, 1033:2, 1035:10, 1039:4, 1040:14, 1041:4, 1042:1, 1045:19, 1045:20, 1047:20, 1062:9, 1075:6, 1075:7, 1075:10, 1075:14, 1075:15, 1075:17, 1076:3, 1076:9, 1076:11, 1079:12, 1085:21, 1086:1, 1086:5, 1089:9, 1090:25, 1091:10, 1091:12, 1100:10, 1105:20, 1110:15, 1118:7, 1119:14, 1133:1, 1133:3, 1133:5, 1133:6, 1135:9, 1139:9, 1139:16, 1146:5, 1146:11, 1146:15, 1146:21, 1146:22, 1147:2, 1147:5, 1147:11, 1148:1, 1148:15, 1151:12, 1151:15, 1152:25, 1153:8, 1154:3, 1154:23, 1155:13, 1155:24</p> <p><b>Drugs</b> [1] - 1061:20</p> <p><b>DTX</b> [1] - 1149:18</p> <p><b>DTX-155</b> [1] - 1204:25</p> <p><b>DTX-16</b> [9] - 1034:13, 1034:24, 1035:6, 1035:7, 1036:1, 1049:16, 1050:1, 1061:17, 1063:8</p> <p><b>DTX-16</b> [1] - 1035:3</p> <p><b>DTX-16.3</b> [1] - 1106:19</p> <p><b>DTX-16.4</b> [1] - 1063:25</p> <p><b>DTX-16.6</b> [2] - 1068:21, 1103:6</p> <p><b>DTX-24</b> [4] - 1042:16, 1042:22, 1042:25, 1047:14</p> <p><b>DTX-28</b> [3] - 1043:23, 1044:6, 1044:10</p> <p><b>DTX-301</b> [1] - 1006:16</p> <p><b>DTX-397</b> [2] - 1219:9, 1219:13</p> <p><b>DTX-398</b> [4] - 1025:24, 1026:4, 1026:8, 1026:10</p> <p><b>DTX-411</b> [2] - 1008:5, 1019:23</p> <p><b>DTX-6.11</b> [1] - 1040:6</p> <p><b>DTX-9</b> [7] - 1032:8,</p>	<p>1032:17, 1032:21, 1042:17, 1047:14, 1149:8, 1149:9</p> <p><b>DTX-9.7</b> [2] - 1149:16, 1149:20</p> <p><b>DTZ-155</b> [1] - 1205:7</p> <p><b>Dual</b> [1] - 1159:24</p> <p><b>Dual-Melatonin</b> [1] - 1159:24</p> <p><b>duct</b> [1] - 1076:4</p> <p><b>due</b> [1] - 1269:8</p> <p><b>duly</b> [1] - 1126:12</p> <p><b>dunk</b> [1] - 1268:11</p> <p><b>during</b> [19] - 1010:10, 1152:24, 1153:8, 1165:2, 1165:6, 1165:7, 1166:18, 1166:22, 1166:24, 1167:5, 1167:13, 1167:25, 1168:12, 1171:5, 1183:25, 1193:7, 1203:5, 1227:20, 1228:7</p> <p style="text-align: center;"><b>E</b></p> <p><b>early</b> [6] - 1093:23, 1098:19, 1160:11, 1218:15, 1218:18, 1262:20</p> <p><b>easier</b> [2] - 1260:3, 1263:18</p> <p><b>eastman</b> [2] - 1181:13, 1181:16</p> <p><b>Eastman's</b> [1] - 1169:21</p> <p><b>eat</b> [5] - 1184:22, 1185:3, 1185:6, 1185:8, 1185:25</p> <p><b>edited</b> [1] - 1247:16</p> <p><b>editor</b> [2] - 1027:11, 1027:13</p> <p><b>editor-in-chief</b> [1] - 1027:13</p> <p><b>editorial</b> [1] - 1027:16</p> <p><b>education</b> [1] - 1026:11</p> <p><b>educational</b> [1] - 1163:13</p> <p><b>effect</b> [20] - 1035:12, 1041:17, 1133:21, 1135:25, 1140:25, 1150:23, 1174:22, 1175:18, 1175:20, 1176:18, 1181:5, 1189:13, 1189:20, 1200:17, 1201:18, 1204:12, 1204:14, 1204:15, 1211:3, 1262:4</p>	<p><b>effective</b> [10] - 1044:12, 1175:8, 1194:20, 1208:11, 1208:17, 1209:24, 1217:7, 1217:21, 1219:6</p> <p><b>effectively</b> [3] - 1042:3, 1214:19, 1217:15</p> <p><b>effectiveness</b> [1] - 1185:9</p> <p><b>effects</b> [12] - 1026:22, 1106:4, 1106:6, 1129:12, 1129:14, 1161:16, 1182:6, 1188:5, 1190:2, 1199:1, 1199:4, 1210:23</p> <p><b>Effects</b> [1] - 1068:23</p> <p><b>efficacious</b> [1] - 1186:14</p> <p><b>efficacy</b> [9] - 1046:17, 1047:3, 1047:18, 1135:16, 1135:17, 1208:24, 1209:19, 1210:20, 1210:21</p> <p><b>efficient</b> [1] - 1223:12</p> <p><b>eight</b> [2] - 1031:21, 1193:7</p> <p><b>either</b> [5] - 1032:5, 1033:8, 1093:10, 1103:13, 1111:21</p> <p><b>EKINER</b> [1] - 1005:15</p> <p><b>elaborate</b> [1] - 1183:11</p> <p><b>element</b> [2] - 1182:12, 1235:2</p> <p><b>elements</b> [9] - 1049:13, 1051:5, 1051:24, 1055:16, 1055:17, 1057:16, 1057:22, 1057:23, 1194:25</p> <p><b>elicit</b> [4] - 1105:25, 1177:4, 1182:4, 1183:6</p> <p><b>elicited</b> [3] - 1015:9, 1015:25, 1223:4</p> <p><b>eliminate</b> [2] - 1046:17, 1048:17</p> <p><b>eliminated</b> [3] - 1133:1, 1133:4, 1134:15</p> <p><b>eliminates</b> [1] - 1048:15</p> <p><b>elimination</b> [3] - 1037:16, 1132:16, 1132:17</p> <p><b>elsewhere</b> [1] - 1080:21</p>	<p><b>eluded</b> [1] - 1016:12</p> <p><b>emanating</b> [1] - 1203:18</p> <p><b>embodiment</b> [6] - 1020:8, 1243:8, 1245:7, 1245:13, 1253:4, 1256:10</p> <p><b>Embodiment</b> [1] - 1008:17</p> <p><b>embodiments</b> [3] - 1237:5, 1241:12, 1252:24</p> <p><b>embody</b> [1] - 1241:11</p> <p><b>embrace</b> [1] - 1252:2</p> <p><b>embraced</b> [1] - 1171:10</p> <p><b>Emens</b> [33] - 1120:22, 1167:11, 1167:17, 1168:7, 1171:7, 1171:10, 1171:14, 1173:17, 1173:20, 1174:9, 1174:13, 1175:14, 1183:21, 1199:17, 1199:19, 1200:4, 1204:21, 1205:21, 1206:4, 1207:7, 1215:19, 1215:21, 1216:1, 1216:8, 1217:1, 1217:3, 1217:24, 1218:11, 1218:21, 1219:15, 1220:18, 1228:9, 1258:1</p> <p><b>Emens'</b> [1] - 1172:10</p> <p><b>Emens's</b> [1] - 1219:9</p> <p><b>employed</b> [1] - 1115:21</p> <p><b>employee</b> [1] - 1040:2</p> <p><b>employees</b> [2] - 1113:5, 1113:8</p> <p><b>Employment</b> [1] - 1127:22</p> <p><b>empties</b> [1] - 1030:22</p> <p><b>enable</b> [1] - 1228:25</p> <p><b>Encyclopedia</b> [1] - 1054:23</p> <p><b>end</b> [26] - 1020:14, 1021:4, 1031:16, 1034:4, 1053:24, 1078:9, 1130:4, 1168:1, 1168:11, 1205:4, 1223:8, 1231:24, 1232:2, 1233:1, 1233:4, 1233:9, 1234:4, 1234:19, 1234:23, 1235:1, 1235:2, 1235:19, 1235:22, 1243:12, 1243:13, 1266:16</p>	<p><b>ended</b> [1] - 1168:4</p> <p><b>endogenous</b> [1] - 1176:2</p> <p><b>endogenously</b> [1] - 1203:4</p> <p><b>ends</b> [1] - 1096:22</p> <p><b>Engel</b> [3] - 1136:7, 1138:1, 1138:2</p> <p><b>engineered</b> [2] - 1033:11, 1114:18</p> <p><b>England</b> [1] - 1173:11</p> <p><b>English</b> [1] - 1255:4</p> <p><b>enormous</b> [1] - 1262:24</p> <p><b>enrollees</b> [1] - 1219:18</p> <p><b>enter</b> [4] - 1014:5, 1030:24, 1269:14, 1270:1</p> <p><b>entered</b> [3] - 1032:18, 1034:24, 1042:21</p> <p><b>entertaining</b> [1] - 1271:23</p> <p><b>entire</b> [5] - 1096:13, 1183:20, 1203:22, 1228:5, 1254:17</p> <p><b>entirety</b> [1] - 1032:5</p> <p><b>entitled</b> [4] - 1062:4, 1094:5, 1115:8, 1150:22</p> <p><b>entity</b> [1] - 1034:7</p> <p><b>entrain</b> [7] - 1194:20, 1197:10, 1197:17, 1217:15, 1218:1, 1218:16, 1218:19</p> <p><b>entrained</b> [8] - 1171:5, 1195:9, 1196:7, 1197:18, 1208:20, 1208:21, 1218:8, 1218:11</p> <p><b>entraining</b> [15] - 1191:4, 1191:9, 1192:16, 1193:23, 1195:7, 1195:15, 1195:24, 1196:5, 1196:8, 1197:16, 1198:2, 1198:5, 1198:7, 1208:18, 1209:22</p> <p><b>entrainment</b> [18] - 1173:5, 1178:12, 1191:1, 1192:7, 1192:9, 1193:16, 1194:18, 1195:2, 1195:5, 1196:1, 1196:17, 1196:19, 1196:23, 1197:20, 1204:16, 1223:23, 1224:20</p> <p><b>entry</b> [1] - 1127:22</p>
--	--	---	---	---

<p><b>environment</b> [1] - 1170:15</p> <p><b>enzyme</b> [37] - 1030:18, 1031:17, 1032:3, 1032:25, 1040:23, 1041:19, 1051:9, 1051:20, 1053:25, 1054:3, 1065:18, 1065:20, 1065:22, 1066:13, 1067:19, 1068:2, 1078:8, 1078:25, 1085:16, 1085:18, 1085:20, 1093:16, 1097:13, 1097:23, 1131:16, 1132:4, 1132:6, 1132:9, 1132:14, 1133:23, 1135:23, 1136:24, 1141:13, 1141:17, 1143:19, 1145:24, 1189:9</p> <p><b>enzymes</b> [81] - 1031:1, 1031:3, 1031:5, 1031:8, 1031:11, 1031:13, 1031:15, 1031:19, 1031:20, 1031:23, 1033:6, 1033:10, 1033:11, 1034:6, 1034:9, 1039:1, 1039:4, 1039:5, 1040:22, 1041:12, 1041:18, 1041:20, 1042:9, 1048:7, 1061:1, 1065:9, 1065:21, 1066:5, 1066:18, 1066:20, 1067:6, 1067:12, 1067:25, 1068:1, 1069:17, 1073:9, 1074:6, 1074:11, 1074:13, 1075:11, 1075:14, 1078:5, 1078:11, 1078:13, 1078:21, 1081:16, 1081:25, 1082:3, 1082:7, 1084:15, 1085:15, 1090:7, 1090:23, 1092:20, 1096:12, 1096:13, 1104:25, 1116:18, 1131:3, 1131:23, 1132:3, 1133:7, 1133:8, 1133:9, 1136:20, 1136:22, 1136:23, 1141:11, 1141:20, 1142:6, 1146:10, 1147:10, 1147:21, 1148:1, 1148:2, 1148:9,</p>	<p>1148:14, 1159:4, 1160:13, 1161:2</p> <p><b>epidemic</b> [1] - 1185:13</p> <p><b>episode</b> [5] - 1173:8, 1183:4, 1183:20, 1183:23, 1203:8</p> <p><b>equal</b> [2] - 1097:14, 1133:15</p> <p><b>equally</b> [1] - 1243:22</p> <p><b>equals</b> [1] - 1021:23</p> <p><b>equipoise</b> [4] - 1245:2, 1247:9, 1248:10, 1248:14</p> <p><b>equivalent</b> [1] - 1267:10</p> <p><b>ERIC</b> [1] - 1005:9</p> <p><b>Eric</b> [1] - 1052:9</p> <p><b>errata</b> [2] - 1270:2, 1271:8</p> <p><b>error</b> [2] - 1023:22, 1243:22</p> <p><b>ESQ</b> [14] - 1005:3, 1005:3, 1005:4, 1005:4, 1005:5, 1005:8, 1005:9, 1005:9, 1005:10, 1005:12, 1005:15, 1005:16, 1005:16, 1005:17</p> <p><b>essay</b> [1] - 1099:22</p> <p><b>essential</b> [1] - 1147:22</p> <p><b>essentially</b> [5] - 1008:17, 1103:18, 1228:24, 1240:11, 1245:18</p> <p><b>establish</b> [3] - 1077:12, 1136:22, 1199:18</p> <p><b>established</b> [4] - 1009:11, 1151:13, 1179:10, 1179:22</p> <p><b>estimate</b> [3] - 1085:15, 1121:18, 1218:10</p> <p><b>et</b> [3] - 1:8, 1034:3, 1042:12</p> <p><b>evaluated</b> [1] - 1208:13</p> <p><b>evaluating</b> [1] - 1041:25</p> <p><b>evaluation</b> [2] - 1208:25, 1209:21</p> <p><b>evening</b> [4] - 1167:15, 1167:23, 1168:2, 1185:3</p> <p><b>evenly</b> [2] - 1121:18, 1122:2</p> <p><b>event</b> [1] - 1056:12</p> <p><b>eventually</b> [1] - 1263:5</p> <p><b>evidence</b> [78] -</p>	<p>1014:11, 1016:1, 1016:4, 1016:8, 1016:17, 1017:19, 1017:24, 1017:25, 1019:2, 1026:5, 1026:8, 1032:18, 1032:21, 1034:25, 1035:3, 1036:25, 1037:3, 1038:1, 1038:11, 1038:15, 1042:21, 1042:23, 1042:25, 1043:1, 1044:10, 1048:23, 1049:1, 1049:23, 1071:24, 1095:19, 1095:24, 1099:8, 1099:16, 1103:22, 1114:3, 1121:11, 1122:12, 1127:17, 1127:20, 1136:11, 1136:14, 1137:9, 1137:12, 1139:21, 1139:24, 1139:25, 1151:4, 1151:7, 1162:2, 1162:6, 1169:13, 1170:3, 1172:1, 1182:2, 1185:23, 1209:17, 1216:6, 1216:14, 1219:13, 1224:6, 1224:19, 1227:18, 1232:24, 1238:9, 1238:13, 1239:7, 1239:10, 1239:11, 1239:13, 1239:16, 1243:5, 1245:10, 1256:12, 1256:14, 1260:10, 1262:18, 1263:10</p> <p><b>evident</b> [1] - 1118:22</p> <p><b>evidential</b> [1] - 1069:13</p> <p><b>evidentiary</b> [4] - 1123:20, 1124:3, 1124:19, 1124:22</p> <p><b>evidentiary-wise</b> [1] - 1124:3</p> <p><b>evolution</b> [1] - 1185:5</p> <p><b>evolve</b> [1] - 1168:23</p> <p><b>evolved</b> [2] - 1203:8, 1232:4</p> <p><b>exact</b> [3] - 1059:6, 1088:18, 1146:8</p> <p><b>exactly</b> [14] - 1034:9, 1052:21, 1078:22, 1085:17, 1088:7, 1112:15, 1123:21, 1193:11, 1229:1, 1232:3, 1236:13, 1241:15, 1246:3,</p>	<p>1253:9</p> <p><b>EXAMINATION</b> [11] - 1006:7, 1025:8, 1052:7, 1116:6, 1126:14, 1142:16, 1162:23, 1190:17, 1214:13, 1216:24, 1220:16</p> <p><b>examination</b> [15] - 1015:13, 1018:4, 1055:5, 1063:13, 1063:23, 1064:18, 1064:25, 1067:10, 1067:17, 1069:23, 1080:1, 1080:16, 1087:17, 1105:13, 1156:25</p> <p><b>examine</b> [4] - 1022:25, 1056:15, 1136:19, 1161:16</p> <p><b>examined</b> [1] - 1131:2</p> <p><b>example</b> [34] - 1017:16, 1022:8, 1029:18, 1053:23, 1054:21, 1054:25, 1055:16, 1075:21, 1076:11, 1139:13, 1167:13, 1191:11, 1191:12, 1191:25, 1195:20, 1218:10, 1229:2, 1230:2, 1232:9, 1234:10, 1234:22, 1237:9, 1241:11, 1242:11, 1242:12, 1242:14, 1243:12, 1243:19, 1243:21, 1243:25, 1253:4, 1253:6, 1256:20</p> <p><b>examples</b> [5] - 1138:16, 1139:5, 1233:11, 1242:15, 1252:25</p> <p><b>except</b> [2] - 1193:9, 1243:19</p> <p><b>excerpt</b> [1] - 1170:8</p> <p><b>excerpts</b> [1] - 1130:2</p> <p><b>exclude</b> [3] - 1060:21, 1116:19, 1252:23</p> <p><b>excluded</b> [2] - 1104:24, 1116:17</p> <p><b>exclusively</b> [1] - 1061:3</p> <p><b>excrete</b> [1] - 1075:19</p> <p><b>excreted</b> [6] - 1075:25, 1076:4, 1076:13, 1077:23, 1077:24, 1133:5</p> <p><b>excuse</b> [2] - 1122:5, 1170:9</p>	<p><b>excused</b> [5] - 1014:13, 1120:8, 1162:15, 1162:17, 1215:14</p> <p><b>exercise</b> [1] - 1059:17</p> <p><b>exhausted</b> [1] - 1205:24</p> <p><b>Exhibit</b> [1] - 1169:10</p> <p><b>exhibit</b> [8] - 1068:22, 1095:1, 1114:14, 1115:3, 1115:7, 1264:9, 1265:16</p> <p><b>exhibits</b> [6] - 1014:5, 1108:8, 1169:2, 1265:12, 1269:18, 1269:20</p> <p><b>exist</b> [1] - 1042:6</p> <p><b>existence</b> [1] - 1070:22</p> <p><b>exists</b> [4] - 1090:15, 1101:3, 1230:13, 1231:8</p> <p><b>exits</b> [1] - 1097:19</p> <p><b>exoenzymes</b> [3] - 1064:22, 1065:6, 1069:20</p> <p><b>expect</b> [7] - 1021:11, 1021:13, 1022:1, 1105:10, 1191:18, 1205:25, 1256:6</p> <p><b>expectation</b> [9] - 1143:5, 1143:10, 1143:25, 1144:13, 1144:23, 1145:4, 1198:11, 1198:15, 1198:24</p> <p><b>expected</b> [6] - 1048:4, 1048:8, 1052:2, 1092:1, 1205:21, 1206:7</p> <p><b>experience</b> [7] - 1013:11, 1026:11, 1029:13, 1045:13, 1069:10, 1105:18, 1113:22</p> <p><b>experiment</b> [4] - 1081:5, 1131:15, 1132:1, 1171:6</p> <p><b>experimental</b> [2] - 1043:9, 1076:24</p> <p><b>experiments</b> [3] - 1080:17, 1083:5, 1148:16</p> <p><b>expert</b> [17] - 1013:14, 1024:22, 1028:6, 1110:21, 1120:1, 1128:22, 1130:13, 1163:1, 1238:22, 1238:25, 1239:3, 1239:8, 1245:11, 1245:12, 1254:15,</p>
---	---	---	--	---



1264:14, 1264:17 <b>expertise</b> [2] - 1029:10, 1188:25 <b>experts</b> [2] - 1174:6, 1247:17 <b>experts'</b> [1] - 1216:2 <b>explain</b> [6] - 1048:11, 1056:19, 1061:10, 1090:2, 1166:16, 1243:25 <b>explained</b> [5] - 1187:2, 1202:13, 1204:3, 1228:10, 1243:22 <b>explaining</b> [5] - 1046:8, 1132:18, 1187:17, 1203:13, 1203:22 <b>explains</b> [1] - 1189:25 <b>explicitly</b> [2] - 1061:13, 1067:18 <b>explode</b> [1] - 1247:17 <b>explosion</b> [1] - 1236:20 <b>exposure</b> [17] - 1044:24, 1047:3, 1048:1, 1048:3, 1129:12, 1129:15, 1132:10, 1133:21, 1135:13, 1135:14, 1135:18, 1140:11, 1140:14, 1141:1, 1151:14, 1152:2, 1152:6 <b>expressed</b> [3] - 1033:11, 1174:6, 1192:6 <b>expressing</b> [2] - 1075:1, 1114:19 <b>expression</b> [5] - 1041:19, 1081:8, 1081:13, 1082:3, 1083:6 <b>expressly</b> [4] - 1191:4, 1191:8, 1195:15, 1198:2 <b>extended</b> [1] - 1194:7 <b>extension</b> [1] - 1269:8 <b>extensions</b> [1] - 1267:18 <b>extensively</b> [1] - 1027:20 <b>extent</b> [3] - 1044:24, 1159:8, 1237:2 <b>extraordinary</b> [1] - 1173:20 <b>extreme</b> [1] - 1119:10 <b>extrinsic</b> [7] - 1238:9, 1238:13, 1239:7, 1239:11, 1243:5,	1245:10, 1256:12  <b>F</b>  <b>face</b> [1] - 1177:5 <b>facial</b> [2] - 1014:23, 1015:1 <b>facilitate</b> [1] - 1269:22 <b>fact</b> [35] - 1012:1, 1013:20, 1016:13, 1043:7, 1062:18, 1071:12, 1072:20, 1072:25, 1079:12, 1087:9, 1093:14, 1098:25, 1101:9, 1105:2, 1108:12, 1118:15, 1136:23, 1139:10, 1142:10, 1155:23, 1179:2, 1180:22, 1182:5, 1185:24, 1193:14, 1204:20, 1209:21, 1213:2, 1214:21, 1243:22, 1251:9, 1255:11, 1255:18, 1263:13, 1267:20 <b>factor</b> [2] - 1035:24, 1245:19 <b>facts</b> [1] - 1251:24 <b>factual</b> [2] - 1258:6, 1264:12 <b>faculty</b> [1] - 1185:1 <b>failed</b> [9] - 1139:20, 1182:24, 1183:3, 1184:4, 1203:22, 1203:23, 1211:8, 1214:21, 1243:2 <b>failure</b> [1] - 1187:7 <b>fair</b> [26] - 1007:13, 1011:22, 1056:14, 1058:24, 1059:21, 1063:10, 1068:15, 1085:4, 1092:16, 1094:24, 1098:17, 1110:23, 1110:25, 1117:22, 1117:23, 1164:7, 1190:24, 1198:20, 1207:5, 1212:3, 1214:4, 1216:11, 1221:1, 1233:6, 1244:14, 1259:4 <b>fairest</b> [1] - 1019:3 <b>fairly</b> [2] - 1085:22, 1235:15 <b>fairness</b> [2] - 1087:16, 1210:4 <b>fairway</b> [1] - 1232:1 <b>fall</b> [4] - 1168:8, 1179:23, 1224:11,	1267:23 <b>fallback</b> [1] - 1247:11 <b>falling</b> [1] - 1187:4 <b>false</b> [1] - 1104:3 <b>familiar</b> [9] - 1076:19, 1128:8, 1165:22, 1168:20, 1182:21, 1184:6, 1209:11, 1246:8, 1256:3 <b>families</b> [2] - 1167:24, 1182:9 <b>family</b> [4] - 1031:13, 1031:19, 1075:11, 1096:14 <b>famous</b> [1] - 1237:22 <b>far</b> [6] - 1040:15, 1070:11, 1073:11, 1077:4, 1197:2, 1250:15 <b>fashion</b> [1] - 1016:8 <b>fast</b> [1] - 1033:6 <b>faster</b> [2] - 1142:5 <b>fathom</b> [1] - 1186:23 <b>faulting</b> [1] - 1240:6 <b>favor</b> [2] - 1084:24, 1225:23 <b>FDA</b> [49] - 1013:12, 1013:15, 1022:25, 1033:2, 1033:20, 1033:21, 1041:23, 1043:7, 1043:16, 1045:21, 1046:1, 1080:16, 1093:20, 1094:14, 1095:3, 1095:4, 1100:22, 1119:8, 1119:15, 1143:9, 1143:12, 1143:13, 1143:16, 1143:24, 1144:12, 1144:13, 1144:25, 1148:7, 1158:20, 1158:23, 1159:12, 1186:17, 1186:19, 1198:14, 1198:17, 1207:16, 1208:10, 1211:22, 1215:8, 1218:23, 1221:6, 1260:4, 1260:9, 1260:19, 1262:13, 1262:19, 1263:4, 1263:5, 1263:14 <b>FDA's</b> [1] - 1221:7 <b>February</b> [1] - 1159:12 <b>feces</b> [5] - 1076:5, 1076:8, 1077:24, 1133:6, 1134:14 <b>Federal</b> [4] - 1228:24, 1251:21, 1252:7, 1256:7 <b>federal</b> [1] - 1251:22	<b>feet</b> [1] - 1030:16 <b>fellow</b> [1] - 1163:20 <b>fellowship</b> [1] - 1026:19 <b>felt</b> [10] - 1116:14, 1186:6, 1187:7, 1187:16, 1217:7, 1222:2, 1223:2, 1223:5, 1224:6, 1224:19 <b>fence</b> [1] - 1070:7 <b>few</b> [3] - 1017:3, 1164:5, 1166:6 <b>fewer</b> [1] - 1015:15 <b>field</b> [6] - 1023:9, 1027:20, 1028:6, 1098:18, 1171:7, 1245:19 <b>fifth</b> [2] - 1144:17, 1181:4 <b>fight</b> [1] - 1123:20 <b>Figure</b> [1] - 1095:9 <b>figure</b> [9] - 1021:18, 1059:23, 1095:10, 1098:19, 1122:10, 1194:14, 1194:15, 1205:20, 1234:16 <b>figured</b> [1] - 1218:19 <b>file</b> [2] - 1265:17, 1269:14 <b>filed</b> [2] - 1216:3, 1261:3 <b>filing</b> [1] - 1271:11 <b>fill</b> [2] - 1048:4, 1112:24 <b>final</b> [3] - 1057:1, 1162:19, 1188:1 <b>finalized</b> [2] - 1094:21, 1261:15 <b>finalizes</b> [1] - 1094:15 <b>finalizing</b> [1] - 1265:14 <b>findings</b> [5] - 1141:6, 1155:4, 1164:1, 1221:23, 1269:1 <b>fine</b> [9] - 1100:17, 1101:19, 1126:2, 1158:18, 1197:19, 1237:19, 1238:2, 1249:11, 1249:15 <b>fingertips</b> [1] - 1092:9 <b>finish</b> [1] - 1066:25 <b>finished</b> [2] - 1267:1, 1268:23 <b>fire</b> [1] - 1012:11 <b>first</b> [55] - 1007:15, 1014:16, 1020:21, 1020:23, 1030:7, 1030:15, 1031:12, 1040:13, 1061:12,	1061:17, 1066:13, 1069:5, 1082:17, 1096:4, 1096:7, 1101:22, 1112:10, 1122:15, 1126:12, 1131:22, 1135:4, 1141:11, 1143:12, 1147:20, 1160:10, 1164:14, 1164:20, 1169:5, 1172:14, 1173:2, 1173:5, 1177:3, 1177:18, 1186:10, 1189:1, 1194:6, 1195:20, 1214:22, 1215:3, 1216:1, 1225:3, 1229:16, 1229:19, 1230:19, 1231:16, 1235:13, 1238:8, 1251:11, 1255:9, 1265:7, 1265:8, 1265:23, 1266:2, 1266:6, 1268:18 <b>first-pass</b> [1] - 1030:7 <b>fit</b> [2] - 1154:24, 1167:6 <b>five</b> [28] - 1019:13, 1067:6, 1125:21, 1151:14, 1152:1, 1152:6, 1174:4, 1175:10, 1176:6, 1178:11, 1179:13, 1179:24, 1185:24, 1206:7, 1234:8, 1235:9, 1235:12, 1235:23, 1236:10, 1236:12, 1237:17, 1243:13, 1243:14, 1254:9, 1254:10, 1256:10, 1260:5 <b>five-fold</b> [4] - 1151:14, 1152:1, 1152:6 <b>fivefold</b> [1] - 1045:22 <b>flew</b> [1] - 1179:16 <b>flow</b> [7] - 1096:3, 1096:7, 1096:8, 1096:22, 1097:5, 1101:22, 1233:24 <b>fluctuates</b> [1] - 1214:7 <b>fluvoxamine</b> [19] - 1043:6, 1043:18, 1044:20, 1044:23, 1045:25, 1046:19, 1048:2, 1048:14, 1060:2, 1060:7, 1060:10, 1100:15, 1117:3, 1117:11, 1149:5, 1150:24, 1151:19, 1154:6, 1161:17
--	---	---	---	--

<p><b>focus</b> [5] - 1016:16, 1085:3, 1163:23, 1173:24, 1205:2</p> <p><b>focuses</b> [1] - 1163:24</p> <p><b>fold</b> [4] - 1151:14, 1152:1, 1152:6</p> <p><b>follow</b> [10] - 1008:22, 1015:18, 1094:20, 1126:24, 1127:2, 1208:2, 1231:7, 1256:16, 1259:2, 1270:13</p> <p><b>follow-on</b> [3] - 1126:24, 1127:2, 1259:2</p> <p><b>followed</b> [3] - 1050:8, 1161:7, 1255:19</p> <p><b>following</b> [9] - 1006:3, 1050:10, 1054:19, 1074:5, 1092:18, 1153:23, 1163:22, 1196:10, 1272:2</p> <p><b>follows</b> [9] - 1014:25, 1054:10, 1107:5, 1126:13, 1162:22, 1215:22, 1230:3, 1235:7, 1255:23</p> <p><b>food</b> [8] - 1184:17, 1188:5, 1188:7, 1189:13, 1189:16, 1189:20, 1189:21, 1190:11</p> <p><b>Fools</b> [1] - 1267:16</p> <p><b>fools</b> [1] - 1267:17</p> <p><b>footballers</b> [1] - 1177:25</p> <p><b>FOR</b> [1] - 1:3</p> <p><b>forces</b> [1] - 1217:20</p> <p><b>foreclosed</b> [1] - 1239:13</p> <p><b>foregoing</b> [1] - 1272:4</p> <p><b>forget</b> [3] - 1029:23, 1102:24, 1243:23</p> <p><b>forgive</b> [5] - 1052:17, 1063:6, 1240:15, 1240:18, 1246:6</p> <p><b>forgot</b> [2] - 1169:4, 1244:1</p> <p><b>form</b> [7] - 1007:12, 1166:2, 1228:23, 1230:13, 1235:21, 1241:10, 1251:3</p> <p><b>formation</b> [5] - 1135:6, 1135:7, 1138:4, 1138:7, 1161:4</p> <p><b>formed</b> [2] - 1033:6, 1080:23</p> <p><b>forming</b> [11] - 1011:17, 1032:13,</p>	<p>1034:21, 1037:23, 1040:3, 1072:21, 1136:8, 1137:5, 1165:25, 1169:23, 1198:8</p> <p><b>formula</b> [1] - 1233:16</p> <p><b>formulary</b> [5] - 1220:5, 1220:6, 1220:8, 1220:12, 1221:2</p> <p><b>forth</b> [5] - 1020:19, 1021:10, 1180:10, 1256:8, 1263:5</p> <p><b>forward</b> [3] - 1166:12, 1249:18, 1262:12</p> <p><b>foundation</b> [1] - 1086:12</p> <p><b>founded</b> [1] - 1126:24</p> <p><b>founder</b> [1] - 1126:21</p> <p><b>four</b> [10] - 1066:13, 1066:20, 1067:6, 1092:19, 1092:25, 1093:2, 1131:23, 1186:15, 1205:4</p> <p><b>fourfold</b> [2] - 1044:25, 1045:11</p> <p><b>fraction</b> [1] - 1111:15</p> <p><b>fragments</b> [1] - 1030:13</p> <p><b>frame</b> [1] - 1016:19</p> <p><b>frankly</b> [4] - 1087:16, 1225:16, 1229:24, 1267:8</p> <p><b>free</b> [2] - 1171:5, 1200:1</p> <p><b>free-running</b> [1] - 1171:5</p> <p><b>fresh</b> [1] - 1257:8</p> <p><b>Friday</b> [1] - 1269:16</p> <p><b>friend</b> [1] - 1056:4</p> <p><b>front</b> [5] - 1015:7, 1126:16, 1144:5, 1165:19, 1169:1</p> <p><b>full</b> [9] - 1025:12, 1025:21, 1038:24, 1082:4, 1128:2, 1160:10, 1185:25, 1262:14, 1269:18</p> <p><b>fully</b> [2] - 1219:24, 1257:17</p> <p><b>function</b> [3] - 1165:6, 1168:12, 1190:7</p> <p><b>functional</b> [1] - 1141:17</p> <p><b>fundamental</b> [1] - 1167:9</p> <p><b>funded</b> [1] - 1160:6</p> <p><b>funny</b> [1] - 1267:24</p> <p><b>furthermore</b> [1] - 1218:18</p> <p><b>future</b> [1] - 1270:23</p>	<p><b>G</b></p> <p><b>game</b> [1] - 1056:14</p> <p><b>GARRISON</b> [1] - 1005:8</p> <p><b>gas</b> [1] - 1235:22</p> <p><b>gastrointestinal</b> [1] - 1051:18</p> <p><b>Gateway</b> [1] - 1252:21</p> <p><b>gather</b> [1] - 1072:17</p> <p><b>gathered</b> [2] - 1152:24, 1153:7</p> <p><b>gears</b> [1] - 1140:2</p> <p><b>gender</b> [1] - 1106:5</p> <p><b>General</b> [1] - 1026:19</p> <p><b>general</b> [12] - 1030:24, 1034:19, 1038:21, 1069:9, 1083:11, 1094:16, 1124:21, 1152:25, 1153:8, 1256:3, 1257:25, 1262:4</p> <p><b>generally</b> [4] - 1045:15, 1159:2, 1184:24, 1258:11</p> <p><b>generate</b> [1] - 1021:7</p> <p><b>generic</b> [1] - 1249:14</p> <p><b>genetic</b> [1] - 1065:16</p> <p><b>genetically</b> [2] - 1033:11, 1114:18</p> <p><b>genetics</b> [1] - 1033:17</p> <p><b>German</b> [2] - 1062:1, 1077:4</p> <p><b>GI</b> [1] - 1030:21</p> <p><b>gibberish</b> [1] - 1254:24</p> <p><b>gigantic</b> [1] - 1044:23</p> <p><b>given</b> [23] - 1019:9, 1041:4, 1044:17, 1044:20, 1044:23, 1046:11, 1046:12, 1048:5, 1049:10, 1056:4, 1100:23, 1144:17, 1173:6, 1173:10, 1175:10, 1176:6, 1177:10, 1183:3, 1203:14, 1204:7, 1225:17, 1253:7, 1270:4</p> <p><b>glass</b> [2] - 1076:22, 1077:2</p> <p><b>goal</b> [10] - 1192:8, 1192:11, 1192:12, 1192:18, 1193:9, 1193:13, 1193:20, 1194:2, 1194:10, 1201:1</p> <p><b>God</b> [1] - 1122:7</p> <p><b>gotcha</b> [1] - 1120:17</p> <p><b>Government</b> [1] -</p>	<p>1163:21</p> <p><b>grade</b> [3] - 1013:2, 1013:6, 1013:9</p> <p><b>gradually</b> [2] - 1183:16, 1202:16</p> <p><b>graduated</b> [2] - 1026:13, 1163:15</p> <p><b>grammar</b> [2] - 1251:16, 1255:16</p> <p><b>grant</b> [1] - 1269:8</p> <p><b>graph</b> [7] - 1043:23, 1044:14, 1044:16, 1044:21, 1176:12, 1178:15, 1201:4</p> <p><b>great</b> [5] - 1174:13, 1217:11, 1226:8, 1226:15, 1265:15</p> <p><b>greater</b> [6] - 1079:10, 1097:14, 1097:24, 1132:15, 1133:14, 1151:14</p> <p><b>Greenblatt</b> [27] - 1023:19, 1025:10, 1025:13, 1025:15, 1025:20, 1025:23, 1026:12, 1026:21, 1027:5, 1027:24, 1028:6, 1028:13, 1030:5, 1052:9, 1064:4, 1068:7, 1080:14, 1089:7, 1106:22, 1115:11, 1116:8, 1128:4, 1137:4, 1138:24, 1149:12, 1188:18, 1189:1</p> <p><b>Greenblatt's</b> [5] - 1129:16, 1138:10, 1143:4, 1147:18, 1148:7</p> <p><b>GRETKOWSKI</b> [1] - 1005:17</p> <p><b>grind</b> [1] - 1034:4</p> <p><b>Groombridge</b> [4] - 1172:2, 1207:3, 1210:8, 1226:19</p> <p><b>GROOMBRIDGE</b> [148] - 1005:8, 1016:6, 1016:24, 1017:15, 1018:2, 1018:5, 1018:9, 1018:13, 1018:16, 1018:23, 1019:4, 1019:9, 1019:13, 1023:20, 1024:8, 1025:3, 1123:7, 1123:11, 1162:19, 1162:24, 1163:5, 1165:15, 1166:10, 1166:15, 1169:9, 1169:14,</p>	<p>1169:25, 1170:4, 1170:6, 1171:22, 1172:4, 1172:6, 1172:8, 1180:5, 1185:19, 1186:1, 1188:12, 1190:14, 1205:22, 1206:3, 1206:7, 1206:9, 1206:12, 1206:21, 1206:24, 1209:15, 1214:14, 1214:24, 1215:15, 1219:11, 1220:17, 1221:12, 1222:3, 1222:5, 1222:8, 1222:14, 1222:16, 1222:20, 1222:24, 1223:3, 1223:13, 1224:8, 1224:21, 1225:4, 1225:7, 1225:12, 1225:16, 1226:3, 1226:20, 1227:3, 1227:5, 1227:8, 1227:11, 1227:22, 1227:24, 1228:3, 1228:17, 1228:20, 1229:13, 1229:18, 1230:7, 1230:16, 1230:21, 1231:17, 1232:13, 1233:15, 1234:1, 1235:11, 1235:13, 1236:12, 1236:23, 1237:2, 1237:6, 1237:24, 1238:10, 1238:16, 1238:21, 1239:2, 1239:12, 1239:17, 1239:23, 1240:8, 1240:14, 1241:19, 1242:1, 1242:5, 1242:9, 1242:12, 1242:18, 1243:9, 1243:20, 1244:2, 1244:6, 1244:8, 1244:14, 1245:4, 1245:21, 1245:24, 1246:3, 1248:24, 1249:5, 1249:9, 1257:5, 1257:13, 1258:17, 1259:13, 1260:2, 1260:15, 1260:22, 1261:3, 1261:8, 1261:17, 1261:20, 1261:23, 1262:2, 1262:10, 1262:20, 1262:23, 1263:16, 1264:3, 1264:5, 1264:10, 1264:20, 1264:25, 1265:20, 1268:3, 1270:10, 1270:21</p>
--	--	---	--	--

<p><b>ground</b> [6] - 1016:4, 1016:18, 1033:9, 1088:6, 1229:21, 1236:16</p> <p><b>group</b> [4] - 1031:15, 1066:13, 1106:13, 1185:1</p> <p><b>Growth</b> [1] - 1027:12</p> <p><b>guaranteeing</b> [1] - 1268:15</p> <p><b>guess</b> [16] - 1008:9, 1181:25, 1191:23, 1223:21, 1223:25, 1224:8, 1225:1, 1227:19, 1229:18, 1249:16, 1253:12, 1254:22, 1258:25, 1263:16, 1264:20, 1266:3</p> <p><b>Guidance</b> [1] - 1094:5</p> <p><b>guidance</b> [9] - 1094:10, 1095:3, 1095:4, 1143:14, 1143:16, 1148:7, 1158:20, 1158:23, 1159:12</p> <p><b>guide</b> [1] - 1256:8</p> <p><b>Guideline</b> [2] - 1012:14, 1012:20</p> <p><b>guideline</b> [1] - 1011:5</p> <p><b>guidelines</b> [2] - 1013:8, 1094:15</p> <p><b>Guidelines</b> [5] - 1010:18, 1010:24, 1011:11, 1012:6, 1013:21</p> <p><b>gut</b> [2] - 1061:4, 1080:20</p> <p><b>guy</b> [1] - 1267:9</p> <p><b>guys</b> [2] - 1206:20, 1225:19</p>	<p>1206:22, 1214:2, 1241:20</p> <p><b>half-life</b> [6] - 1037:17, 1040:10, 1040:18, 1040:19, 1175:5, 1175:6</p> <p><b>half-lives</b> [1] - 1178:10</p> <p><b>hand</b> [11] - 1049:5, 1119:1, 1133:11, 1149:24, 1151:10, 1160:10, 1161:9, 1200:3, 1248:19, 1257:10</p> <p><b>handed</b> [1] - 1124:10</p> <p><b>handling</b> [1] - 1269:22</p> <p><b>happy</b> [5] - 1024:14, 1062:24, 1227:25, 1241:22, 1271:1</p> <p><b>hard</b> [3] - 1186:23, 1259:1, 1265:16</p> <p><b>Harceland</b> [46] - 1036:3, 1036:12, 1049:15, 1049:17, 1050:4, 1053:2, 1054:25, 1061:15, 1061:23, 1061:24, 1064:8, 1066:6, 1066:17, 1067:10, 1067:18, 1069:7, 1069:24, 1070:2, 1070:8, 1071:3, 1071:9, 1071:13, 1072:16, 1074:6, 1074:9, 1092:17, 1100:6, 1102:11, 1102:16, 1102:21, 1103:21, 1106:18, 1108:12, 1108:15, 1108:19, 1108:25, 1109:12, 1109:14, 1116:9, 1129:18, 1130:2, 1130:8, 1140:22, 1140:24, 1184:8</p> <p><b>Harvard</b> [6] - 1026:14, 1026:16, 1026:20, 1163:11, 1163:15, 1163:21</p> <p><b>hassle</b> [2] - 1119:15, 1119:16</p> <p><b>hazard</b> [1] - 1048:16</p> <p><b>hazards</b> [1] - 1042:6</p> <p><b>HCL</b> [2] - 1236:6, 1254:17</p> <p><b>head</b> [4] - 1067:23, 1210:19, 1257:9</p> <p><b>head-to-head</b> [1] - 1210:19</p> <p><b>heading</b> [1] - 1149:25</p> <p><b>headline</b> [1] - 1099:3</p>	<p><b>health</b> [4] - 1118:25, 1119:18, 1119:20, 1163:20</p> <p><b>healthcare</b> [4] - 1219:17, 1219:22, 1219:25, 1220:11</p> <p><b>healthy</b> [3] - 1106:4, 1167:10, 1167:12</p> <p><b>hear</b> [16] - 1055:4, 1091:20, 1093:21, 1096:6, 1097:10, 1149:14, 1187:16, 1217:6, 1218:22, 1230:24, 1245:7, 1245:8, 1249:7, 1257:6, 1260:13, 1263:12</p> <p><b>heard</b> [17] - 1017:3, 1017:7, 1089:2, 1109:21, 1143:5, 1164:7, 1174:22, 1181:7, 1188:21, 1189:2, 1205:22, 1208:19, 1240:5, 1247:16, 1259:15, 1259:20</p> <p><b>hearing</b> [6] - 1121:5, 1121:6, 1165:10, 1186:19, 1226:18, 1227:24</p> <p><b>Hearts</b> [1] - 1251:21</p> <p><b>held</b> [14] - 1006:3, 1014:24, 1019:6, 1054:9, 1058:14, 1120:15, 1123:17, 1157:7, 1211:18, 1223:23, 1267:3, 1268:14, 1268:21, 1269:5</p> <p><b>hello</b> [3] - 1019:21, 1052:9, 1052:11</p> <p><b>help</b> [3] - 1057:15, 1079:21, 1187:21</p> <p><b>helpful</b> [4] - 1057:12, 1174:17, 1174:19, 1257:23</p> <p><b>helping</b> [1] - 1267:10</p> <p><b>helps</b> [1] - 1185:7</p> <p><b>hereby</b> [1] - 1272:4</p> <p><b>herself</b> [1] - 1178:22</p> <p><b>hesitation</b> [1] - 1258:3</p> <p><b>heteroatoms</b> [1] - 1156:21</p> <p><b>Hetlioz</b> [5] - 1207:16, 1207:19, 1214:18, 1214:20, 1262:21</p> <p><b>hi</b> [1] - 1019:20</p> <p><b>hide</b> [1] - 1079:5</p> <p><b>high</b> [17] - 1034:9, 1035:17, 1037:13,</p>	<p>1040:16, 1041:15, 1044:16, 1110:11, 1119:6, 1138:11, 1142:2, 1142:8, 1142:10, 1146:8, 1147:10, 1164:21, 1181:3, 1185:8</p> <p><b>higher</b> [5] - 1108:2, 1172:21, 1185:12, 1190:3, 1194:9</p> <p><b>highlighted</b> [3] - 1064:19, 1066:10, 1269:20</p> <p><b>highly</b> [3] - 1013:2, 1152:19, 1153:3</p> <p><b>hindsight</b> [2] - 1053:15, 1055:21</p> <p><b>history</b> [2] - 1015:9, 1179:6</p> <p><b>hits</b> [1] - 1183:17</p> <p><b>hitting</b> [1] - 1202:10</p> <p><b>hmm</b> [2] - 1195:22, 1197:5</p> <p><b>HOESCHEN</b> [1] - 1005:3</p> <p><b>hold</b> [9] - 1015:11, 1082:5, 1096:18, 1121:14, 1125:14, 1128:1, 1157:3, 1172:2, 1266:20</p> <p><b>hole</b> [1] - 1112:23</p> <p><b>home</b> [4] - 1054:22, 1074:19, 1074:20, 1167:24</p> <p><b>homogenates</b> [1] - 1033:9</p> <p><b>honor</b> [1] - 1085:12</p> <p><b>Honor</b> [156] - 1014:9, 1014:14, 1015:6, 1016:7, 1016:17, 1016:23, 1017:3, 1018:21, 1018:23, 1023:18, 1023:20, 1023:23, 1024:1, 1024:3, 1024:9, 1024:20, 1025:4, 1026:5, 1026:6, 1028:5, 1028:10, 1035:1, 1036:25, 1037:1, 1037:25, 1038:2, 1038:13, 1042:24, 1044:8, 1048:23, 1048:24, 1052:4, 1055:4, 1055:23, 1056:16, 1057:1, 1058:7, 1079:24, 1080:8, 1088:5, 1088:12, 1089:1, 1095:14, 1095:22, 1099:13,</p>	<p>1099:20, 1110:20, 1112:18, 1112:23, 1113:13, 1116:5, 1117:15, 1120:9, 1120:21, 1121:3, 1122:5, 1122:8, 1122:22, 1123:7, 1124:16, 1124:17, 1124:24, 1125:11, 1125:19, 1126:2, 1127:16, 1128:21, 1129:20, 1130:16, 1136:10, 1137:8, 1139:19, 1142:13, 1142:17, 1156:23, 1158:14, 1161:25, 1162:3, 1162:24, 1165:9, 1169:9, 1169:25, 1171:23, 1171:24, 1185:19, 1205:11, 1205:19, 1206:21, 1207:9, 1214:11, 1215:15, 1215:18, 1215:25, 1219:8, 1221:16, 1221:19, 1223:13, 1224:9, 1225:4, 1225:22, 1226:5, 1226:16, 1227:12, 1227:14, 1227:22, 1227:24, 1228:15, 1228:18, 1228:20, 1229:19, 1230:21, 1232:14, 1232:18, 1235:5, 1235:24, 1237:7, 1239:3, 1239:13, 1240:15, 1241:3, 1242:25, 1243:9, 1243:20, 1244:2, 1245:5, 1245:25, 1246:3, 1246:5, 1246:7, 1247:2, 1247:8, 1248:2, 1248:9, 1249:5, 1249:13, 1249:20, 1251:20, 1251:23, 1254:7, 1257:5, 1257:16, 1257:20, 1258:17, 1259:13, 1262:3, 1263:16, 1265:14, 1266:1, 1266:18, 1267:15, 1268:3, 1268:25, 1270:10, 1270:11, 1271:5, 1271:10</p> <p><b>HONORABLE</b> [1] - 1:19</p> <p><b>honored</b> [1] - 1085:11</p> <p><b>hope</b> [2] - 1068:10, 1182:4</p>
<b>H</b>				
<p><b>habitual</b> [4] - 1179:10, 1179:11, 1179:12, 1201:17</p> <p><b>Hack</b> [2] - 1057:20, 1173:14</p> <p><b>half</b> [25] - 1008:16, 1037:17, 1040:10, 1040:18, 1040:19, 1069:5, 1124:3, 1124:20, 1125:6, 1175:5, 1175:6, 1175:10, 1176:6, 1176:20, 1178:10, 1179:14, 1179:25, 1190:7, 1190:9, 1205:16, 1206:17,</p>				

<p><b>hoped</b> [1] - 1205:11</p> <p><b>hopeful</b> [1] - 1125:23</p> <p><b>hopefully</b> [2] - 1134:15, 1169:16</p> <p><b>Hospital</b> [4] - 1026:15, 1026:17, 1026:19, 1163:10</p> <p><b>hospitals</b> [1] - 1219:19</p> <p><b>host</b> [1] - 1016:8</p> <p><b>hour</b> [23] - 1124:3, 1125:4, 1125:6, 1125:13, 1172:16, 1172:18, 1175:6, 1175:12, 1175:15, 1179:14, 1179:25, 1180:14, 1181:21, 1183:3, 1185:25, 1190:1, 1190:8, 1190:9, 1203:6, 1205:16, 1206:17, 1206:22, 1241:20</p> <p><b>hours</b> [34] - 1037:18, 1122:3, 1122:6, 1122:16, 1123:19, 1124:11, 1124:12, 1124:13, 1124:15, 1125:4, 1125:5, 1164:21, 1168:13, 1172:19, 1173:7, 1173:19, 1174:5, 1175:11, 1176:6, 1177:11, 1178:6, 1178:7, 1178:8, 1179:13, 1179:24, 1182:7, 1183:8, 1183:22, 1196:11, 1200:23, 1202:23, 1228:7</p> <p><b>housekeeping</b> [4] - 1219:9, 1221:22, 1222:1, 1225:10</p> <p><b>HPLC</b> [3] - 1022:8, 1022:11, 1022:25</p> <p><b>huge</b> [6] - 1045:8, 1045:22, 1048:1, 1176:18, 1177:1, 1178:11</p> <p><b>human</b> [24] - 1033:3, 1033:9, 1033:19, 1034:3, 1034:7, 1044:25, 1046:21, 1073:22, 1077:9, 1084:16, 1084:18, 1085:17, 1086:1, 1096:11, 1118:9, 1131:2, 1134:12, 1135:24, 1136:22, 1138:18, 1139:7, 1150:23, 1163:24,</p>	<p>1164:14</p> <p><b>humans</b> [7] - 1027:1, 1033:18, 1106:6, 1118:7, 1164:15, 1167:2, 1170:18</p> <p><b>hundreds</b> [1] - 1128:14</p> <p><b>hunger</b> [1] - 1185:2</p> <p><b>hunter</b> [1] - 1028:2</p> <p><b>hurry</b> [1] - 1123:25</p> <p><b>hydride</b> [8] - 1021:4, 1234:11, 1234:24, 1235:14, 1236:5, 1236:17, 1236:19, 1237:8</p> <p><b>hydrochloric</b> [2] - 1234:12, 1234:25</p> <p><b>hydrogen</b> [3] - 1235:22, 1236:19, 1237:10</p> <p><b>hypersensitivity</b> [1] - 1069:13</p> <p><b>hypnotic</b> [1] - 1182:6</p> <p><b>hypothetical</b> [4] - 1059:15, 1059:17, 1072:15, 1102:10</p> <p><b>hypothetically</b> [1] - 1102:9</p>	<p><b>identify</b> [5] - 1038:7, 1113:24, 1259:9, 1259:21, 1263:14</p> <p><b>ignore</b> [1] - 1255:6</p> <p><b>illustrate</b> [1] - 1166:7</p> <p><b>illustrated</b> [4] - 1167:17, 1167:18, 1168:7, 1251:8</p> <p><b>illustration</b> [2] - 1173:16, 1174:19</p> <p><b>imagine</b> [2] - 1201:25, 1242:19</p> <p><b>immediacy</b> [1] - 1257:17</p> <p><b>immediately</b> [2] - 1176:16, 1235:7</p> <p><b>immerse</b> [1] - 1103:25</p> <p><b>impact</b> [4] - 1070:1, 1119:20, 1170:19, 1213:21</p> <p><b>impeaching</b> [1] - 1086:14</p> <p><b>impeachment</b> [1] - 1089:21</p> <p><b>implementation</b> [1] - 1094:13</p> <p><b>Implications</b> [1] - 1094:6</p> <p><b>import</b> [1] - 1054:18</p> <p><b>importance</b> [2] - 1031:2, 1047:16</p> <p><b>important</b> [14] - 1031:19, 1031:22, 1031:24, 1045:20, 1047:18, 1060:22, 1090:3, 1118:25, 1119:18, 1170:20, 1200:21, 1247:25, 1256:18, 1271:25</p> <p><b>importantly</b> [1] - 1094:10</p> <p><b>imposing</b> [1] - 1170:18</p> <p><b>impractical</b> [1] - 1182:7</p> <p><b>impression</b> [1] - 1121:4</p> <p><b>impressive</b> [2] - 1061:25, 1258:9</p> <p><b>imprimatur</b> [1] - 1264:17</p> <p><b>improve</b> [1] - 1217:16</p> <p><b>Impurities</b> [2] - 1261:13, 1261:14</p> <p><b>impurities</b> [30] - 1009:24, 1010:3, 1011:2, 1015:16, 1016:10, 1021:11, 1021:14, 1022:9, 1022:14, 1022:16,</p>	<p>1022:19, 1022:20, 1022:24, 1023:5, 1023:13, 1024:2, 1024:23, 1221:8, 1259:9, 1259:17, 1259:21, 1260:1, 1260:5, 1260:12, 1261:1, 1261:6, 1263:12, 1263:14, 1263:23, 1264:1</p> <p><b>impurity</b> [7] - 1010:5, 1010:23, 1011:11, 1017:13, 1021:12, 1023:10, 1264:2</p> <p><b>IN</b> [2] - 1:2, 1:3</p> <p><b>in-vitro</b> [48] - 1077:13, 1081:5, 1081:18, 1082:7, 1083:5, 1085:14, 1093:20, 1096:10, 1098:15, 1098:16, 1098:19, 1099:22, 1100:7, 1100:11, 1101:1, 1101:10, 1103:22, 1107:12, 1114:17, 1117:18, 1117:19, 1117:20, 1117:25, 1118:3, 1118:12, 1118:14, 1118:17, 1118:23, 1119:6, 1119:12, 1128:8, 1135:22, 1135:24, 1136:7, 1136:19, 1138:1, 1138:8, 1138:17, 1139:14, 1142:11, 1145:15, 1150:6, 1152:20, 1153:4, 1159:2, 1159:7, 1160:11, 1161:1</p> <p><b>inactive</b> [1] - 1141:21</p> <p><b>INC</b> [2] - 1:5, 1:8</p> <p><b>inch</b> [1] - 1254:1</p> <p><b>inclined</b> [1] - 1257:6</p> <p><b>include</b> [5] - 1057:19, 1091:11, 1124:22, 1125:8, 1125:9</p> <p><b>included</b> [4] - 1103:13, 1174:22, 1218:6, 1218:7</p> <p><b>includes</b> [3] - 1028:7, 1192:16, 1262:25</p> <p><b>including</b> [9] - 1068:1, 1096:13, 1105:5, 1107:22, 1161:5, 1163:2, 1171:7, 1171:10, 1223:22</p> <p><b>inconsistent</b> [4] - 1086:17, 1086:22, 1087:5, 1088:21</p>	<p><b>incorporates</b> [1] - 1189:24</p> <p><b>increase</b> [13] - 1039:5, 1041:14, 1045:9, 1045:11, 1045:13, 1045:14, 1045:16, 1048:1, 1051:9, 1051:20, 1116:18, 1152:1, 1152:6</p> <p><b>increased</b> [2] - 1044:25, 1150:6</p> <p><b>increases</b> [2] - 1041:19, 1151:14</p> <p><b>increasing</b> [1] - 1142:3</p> <p><b>incubation</b> [1] - 1074:5</p> <p><b>indexed</b> [1] - 1027:22</p> <p><b>indicated</b> [2] - 1172:9, 1201:16</p> <p><b>indicates</b> [5] - 1035:17, 1140:23, 1155:25, 1201:6, 1251:14</p> <p><b>indicating</b> [1] - 1114:20</p> <p><b>indication</b> [5] - 1021:25, 1022:3, 1207:19, 1220:7, 1223:15</p> <p><b>indications</b> [2] - 1220:9, 1220:13</p> <p><b>indicator</b> [1] - 1021:21</p> <p><b>individual</b> [11] - 1033:10, 1114:19, 1131:2, 1132:3, 1141:17, 1143:19, 1164:20, 1166:19, 1167:14, 1197:17, 1197:18</p> <p><b>individually</b> [1] - 1263:6</p> <p><b>individuals</b> [12] - 1028:3, 1167:4, 1170:24, 1171:4, 1179:4, 1186:12, 1186:25, 1187:16, 1199:23, 1217:17, 1218:12, 1218:16</p> <p><b>induce</b> [2] - 1103:13, 1210:23</p> <p><b>induced</b> [1] - 1116:19</p> <p><b>inducer</b> [18] - 1029:3, 1043:11, 1043:15, 1046:13, 1047:4, 1051:8, 1051:20, 1060:15, 1093:10, 1093:12, 1133:21, 1140:15, 1140:25, 1148:24, 1148:25,</p>
--	--	---	--	---



<p>1149:1, 1155:22, 1159:4 <b>inducers</b> [3] - 1042:9, 1042:13, 1105:11 <b>induction</b> [9] - 1041:16, 1046:19, 1048:3, 1104:11, 1116:17, 1134:19, 1140:11, 1161:17, 1161:19 <b>Industry</b> [1] - 1094:5 <b>industry</b> [3] - 1113:22, 1133:19, 1143:16 <b>ineffective</b> [2] - 1104:12, 1218:24 <b>ineffectiveness</b> [2] - 1041:22, 1047:21 <b>inexpensive</b> [1] - 1118:5 <b>inference</b> [1] - 1050:15 <b>inferred</b> [1] - 1118:12 <b>influence</b> [1] - 1171:3 <b>inform</b> [2] - 1132:10, 1159:8 <b>information</b> [22] - 1012:23, 1033:16, 1036:13, 1042:6, 1051:17, 1066:22, 1072:17, 1082:2, 1082:15, 1090:17, 1104:8, 1104:16, 1117:7, 1118:6, 1118:8, 1134:17, 1135:1, 1145:7, 1155:11, 1172:23, 1260:18, 1262:25 <b>informed</b> [2] - 1229:8, 1229:24 <b>infringed</b> [1] - 1194:16 <b>infringement</b> [8] - 1194:24, 1224:12, 1226:11, 1265:7, 1266:2, 1266:4, 1266:8, 1268:12 <b>ingest</b> [1] - 1075:18 <b>ingredients</b> [1] - 1247:16 <b>inhibit</b> [3] - 1039:4, 1103:13, 1135:12 <b>inhibited</b> [1] - 1138:3 <b>inhibition</b> [9] - 1044:13, 1046:18, 1048:2, 1134:19, 1150:4, 1152:20, 1153:4, 1161:17, 1161:18 <b>inhibition-based</b> [1] - 1150:4 <b>inhibitor</b> [23] -</p>	<p>1028:25, 1041:11, 1043:3, 1043:6, 1043:8, 1043:19, 1049:8, 1049:9, 1051:19, 1060:3, 1093:6, 1100:12, 1100:23, 1101:12, 1102:22, 1133:20, 1137:16, 1138:3, 1141:1, 1148:20, 1155:10, 1155:16, 1159:3 <b>inhibitor's</b> [1] - 1129:12 <b>inhibitors</b> [9] - 1042:9, 1042:13, 1067:15, 1067:19, 1067:20, 1067:21, 1083:10, 1092:15, 1149:5 <b>inhibits</b> [2] - 1069:19, 1103:9 <b>initial</b> [1] - 1245:18 <b>inoperable</b> [2] - 1237:13, 1247:12 <b>inoperative</b> [1] - 1254:23 <b>input</b> [1] - 1243:15 <b>inserts</b> [1] - 1100:14 <b>inside</b> [1] - 1135:24 <b>insofar</b> [2] - 1040:10, 1055:15 <b>insomnia</b> [4] - 1062:6, 1175:13, 1211:23, 1212:4 <b>inspirational</b> [3] - 1208:24, 1209:20, 1209:23 <b>instance</b> [5] - 1014:17, 1202:14, 1243:2, 1264:12, 1265:23 <b>instances</b> [1] - 1217:16 <b>instead</b> [5] - 1172:17, 1183:14, 1233:2, 1252:12, 1270:25 <b>Institute</b> [1] - 1163:21 <b>instruction</b> [2] - 1053:22, 1065:17 <b>instructions</b> [3] - 1007:25, 1008:22, 1015:19 <b>insufficient</b> [1] - 1182:2 <b>insulin</b> [2] - 1185:9, 1185:11 <b>integrated</b> [3] - 1219:22, 1219:24, 1220:11 <b>intended</b> [4] - 1024:5,</p>	<p>1234:20, 1242:21, 1243:23 <b>intent</b> [2] - 1231:20, 1232:22 <b>interact</b> [3] - 1085:21, 1091:10, 1182:9 <b>interacted</b> [2] - 1093:15, 1146:6 <b>interaction</b> [93] - 1028:25, 1029:1, 1029:2, 1041:3, 1041:6, 1041:9, 1044:24, 1045:7, 1045:8, 1045:21, 1045:23, 1045:25, 1046:3, 1046:6, 1046:22, 1048:14, 1048:18, 1050:18, 1050:25, 1051:11, 1051:23, 1052:2, 1057:16, 1057:22, 1060:2, 1060:5, 1060:6, 1060:9, 1060:14, 1060:19, 1076:18, 1077:17, 1077:20, 1085:22, 1086:1, 1086:4, 1089:9, 1090:6, 1090:12, 1090:14, 1090:16, 1090:23, 1090:24, 1091:17, 1091:23, 1092:13, 1093:6, 1093:10, 1096:11, 1101:11, 1104:18, 1105:10, 1110:3, 1116:14, 1116:17, 1118:22, 1119:13, 1127:3, 1127:9, 1128:22, 1134:20, 1135:8, 1135:11, 1135:17, 1135:24, 1137:15, 1138:2, 1138:9, 1138:17, 1138:18, 1139:5, 1139:6, 1143:9, 1143:11, 1143:18, 1143:25, 1144:1, 1144:14, 1144:22, 1144:24, 1145:5, 1145:8, 1145:10, 1155:14, 1155:16, 1155:21, 1158:21, 1188:16, 1188:23, 1189:9, 1250:2 <b>Interaction</b> [1] - 1094:5 <b>Interactions</b> [2] - 1149:25, 1159:24 <b>interactions</b> [34] -</p>	<p>1028:8, 1028:19, 1029:12, 1033:17, 1041:1, 1041:23, 1042:5, 1047:16, 1047:17, 1047:24, 1048:8, 1091:9, 1099:23, 1108:21, 1109:16, 1117:1, 1117:10, 1127:1, 1135:2, 1139:16, 1145:13, 1145:16, 1145:24, 1148:9, 1148:13, 1148:14, 1150:4, 1150:11, 1153:22, 1155:9, 1158:23, 1158:25, 1159:2, 1159:9 <b>interacts</b> [1] - 1032:25 <b>interest</b> [2] - 1160:3, 1166:8 <b>interesting</b> [5] - 1066:24, 1170:11, 1271:22, 1271:23, 1271:24 <b>interject</b> [1] - 1112:25 <b>intermediate</b> [4] - 1251:12, 1251:15, 1252:3, 1252:15 <b>internal</b> [5] - 1026:15, 1114:17, 1164:15, 1168:3, 1202:25 <b>internally</b> [2] - 1113:25, 1220:25 <b>interpret</b> [2] - 1127:9, 1140:21 <b>interpreter</b> [1] - 1229:6 <b>interrupt</b> [2] - 1112:13, 1168:11 <b>interrupted</b> [1] - 1233:24 <b>interval</b> [2] - 1166:18, 1166:20 <b>intervening</b> [1] - 1252:3 <b>intervention</b> [1] - 1190:4 <b>intestines</b> [1] - 1032:2 <b>intrinsic</b> [3] - 1183:7, 1256:12, 1256:14 <b>introduce</b> [2] - 1163:6, 1216:7 <b>introduced</b> [2] - 1216:18, 1264:24 <b>introducing</b> [2] - 1216:5, 1231:19 <b>introduction</b> [2] - 1151:9, 1154:16 <b>invalidated</b> [1] - 1223:25</p>	<p><b>invalidity</b> [11] - 1016:5, 1016:18, 1017:16, 1194:25, 1225:24, 1226:12, 1247:20, 1268:7, 1268:9, 1268:12, 1268:13 <b>invented</b> [1] - 1009:7 <b>invention</b> [5] - 1184:12, 1186:4, 1237:23, 1253:3, 1263:17 <b>inventions</b> [2] - 1073:8, 1198:11 <b>investigate</b> [1] - 1145:15 <b>investigated</b> [2] - 1114:18, 1173:14 <b>Investigational</b> [1] - 1061:20 <b>investigational</b> [7] - 1062:9, 1097:6, 1097:8, 1097:13, 1131:17, 1141:14, 1145:13 <b>investigative</b> [1] - 1180:23 <b>investigator</b> [3] - 1106:14, 1114:4, 1180:24 <b>invokes</b> [1] - 1241:5 <b>involve</b> [1] - 1188:16 <b>involved</b> [15] - 1029:24, 1029:25, 1030:3, 1033:7, 1039:1, 1040:11, 1048:7, 1081:1, 1105:20, 1136:20, 1145:23, 1160:13, 1161:2, 1161:15, 1209:24 <b>involvement</b> [1] - 1161:3 <b>involves</b> [1] - 1174:23 <b>involving</b> [4] - 1015:10, 1154:23, 1188:22, 1189:8 <b>iodomelatonin</b> [1] - 1107:22 <b>ironically</b> [1] - 1202:21 <b>irrespective</b> [1] - 1059:12 <b>isoenzyme</b> [2] - 1049:19, 1068:18 <b>isoenzymes</b> [10] - 1036:9, 1066:8, 1081:1, 1081:9, 1081:13, 1083:6, 1103:8, 1103:9,</p>
---	---	---	--	---

<p>1114:20, 1150:5  <b>isoform</b> [2] - 1131:11,  1131:21  <b>isoforms</b> [2] -  1040:11, 1073:22  <b>isolated</b> [1] - 1033:10  <b>issue</b> [22] - 1015:6,  1015:17, 1017:4,  1130:16, 1174:21,  1181:6, 1223:10,  1223:12, 1224:7,  1224:16, 1225:1,  1226:4, 1226:24,  1227:13, 1229:16,  1237:20, 1244:13,  1245:5, 1247:20,  1264:18, 1270:12,  1271:7  <b>issued</b> [1] - 1217:19  <b>issues</b> [6] - 1028:17,  1121:20, 1129:8,  1164:9, 1271:24,  1271:25  <b>issuing</b> [1] - 1270:11  <b>it'd</b> [1] - 1212:3  <b>item</b> [1] - 1171:13  <b>items</b> [1] - 1169:16  <b>iterations</b> [1] -  1260:17  <b>itself</b> [6] - 1078:23,  1079:2, 1079:9,  1079:13, 1182:21,  1186:22</p>	<p>1005:9  <b>journal</b> [4] - 1027:12,  1027:14, 1062:10,  1062:14  <b>Journal</b> [2] - 1027:14,  1173:11  <b>journals</b> [1] - 1027:16  <b>JTX</b> [1] - 1152:11  <b>JTX-1</b> [1] - 1195:19  <b>JTX-10</b> [1] - 1152:10  <b>JTX-127</b> [3] - 1169:17,  1169:25, 1170:3  <b>JTX-130</b> [4] - 1094:3,  1095:21, 1095:24,  1158:20  <b>JTX-145</b> [3] - 1171:17,  1171:22, 1172:1  <b>JTX-150</b> [5] - 1159:16,  1159:20, 1160:9,  1162:2, 1162:6  <b>JTX-3</b> [1] - 1191:15  <b>JTX-35</b> [9] - 1036:17,  1036:22, 1036:24,  1037:3, 1037:10,  1037:15, 1046:25,  1048:22, 1049:1  <b>JTX-6</b> [1] - 1249:11  <b>JTX-91</b> [6] - 1071:15,  1071:21, 1071:24,  1073:15, 1113:14,  1131:7  <b>JTX-92</b> [3] - 1150:17,  1151:3, 1151:7  <b>JTX-93</b> [9] - 1037:19,  1038:1, 1038:10,  1038:15, 1038:16,  1038:23, 1038:25,  1039:7, 1045:4  <b>JTX-95</b> [6] - 1042:17,  1042:22, 1043:1,  1047:14, 1147:14,  1153:12  <b>Judge</b> [2] - 1:19,  1268:23  <b>judges</b> [1] - 1087:18  <b>judging</b> [1] - 1014:22  <b>judgment</b> [4] -  1221:23, 1225:23,  1268:13  <b>July</b> [4] - 1261:16,  1261:20, 1266:16,  1266:24  <b>jump</b> [1] - 1073:14  <b>jumping</b> [1] - 1074:4  <b>June</b> [1] - 1266:24  <b>junior</b> [1] - 1267:22  <b>jury</b> [2] - 1216:23,  1226:6</p>	<p><b>K</b></p> <p><b>Kansas</b> [2] - 1126:20,  1127:24  <b>KAREN</b> [1] - 1005:12  <b>KAUN</b> [1] - 1005:15  <b>keep</b> [6] - 1066:9,  1142:3, 1142:7,  1165:10, 1185:7,  1245:19  <b>keeping</b> [2] - 1077:5,  1199:25  <b>keeps</b> [1] - 1142:4  <b>KELLER</b> [1] - 1005:2  <b>kept</b> [2] - 1144:19,  1193:19  <b>KERRY</b> [1] - 1005:16  <b>ketoconazole</b> [6] -  1138:3, 1138:12,  1138:21, 1154:14,  1155:5, 1161:19  <b>key</b> [3] - 1133:24,  1145:23, 1153:16  <b>kidney</b> [3] - 1075:25,  1076:7, 1133:4  <b>kill</b> [1] - 1075:24  <b>kind</b> [24] - 1022:25,  1042:5, 1046:10,  1076:16, 1081:15,  1118:20, 1119:21,  1131:1, 1131:12,  1134:8, 1134:17,  1138:17, 1138:18,  1139:5, 1139:6,  1162:13, 1195:11,  1200:21, 1230:25,  1231:25, 1234:15,  1237:11, 1243:17,  1252:18  <b>kindness</b> [1] -  1121:24  <b>kinds</b> [3] - 1060:24,  1081:4, 1097:1  <b>KLEIN</b> [39] - 1005:10,  1126:15, 1127:16,  1127:21, 1128:21,  1129:1, 1129:6,  1129:7, 1129:22,  1129:24, 1130:16,  1130:21, 1130:23,  1132:20, 1132:22,  1134:22, 1134:24,  1136:10, 1136:15,  1137:8, 1137:13,  1137:20, 1137:22,  1139:3, 1139:19,  1140:1, 1140:4,  1140:6, 1140:17,  1140:19, 1141:2,  1141:4, 1142:13,</p>	<p>1151:5, 1156:23,  1157:2, 1158:14,  1161:24, 1162:3  <b>Klein</b> [1] - 1056:2  <b>knowing</b> [7] -  1040:11, 1053:9,  1078:25, 1090:2,  1134:21, 1229:1,  1259:18  <b>knowledge</b> [9] -  1042:19, 1044:4,  1056:23, 1057:3,  1057:8, 1102:14,  1109:17, 1236:15,  1238:12  <b>known</b> [53] - 1011:21,  1017:10, 1036:3,  1037:10, 1037:16,  1038:22, 1040:7,  1040:13, 1042:10,  1042:11, 1043:3,  1043:14, 1043:18,  1046:5, 1047:23,  1048:15, 1049:24,  1053:9, 1053:24,  1055:1, 1063:10,  1064:9, 1068:25,  1069:14, 1092:23,  1098:6, 1098:7,  1105:5, 1111:21,  1111:22, 1111:24,  1116:21, 1117:1,  1134:3, 1141:18,  1145:18, 1145:23,  1146:4, 1146:13,  1146:20, 1147:9,  1148:19, 1148:22,  1148:23, 1149:4,  1151:13, 1153:21,  1156:3, 1156:7,  1177:7, 1181:18,  1204:12  <b>known..</b> [1] - 1153:20  <b>knows</b> [3] - 1185:5,  1210:9, 1216:23  <b>KSR</b> [1] - 1057:4</p>	<p><b>lack</b> [2] - 1190:25,  1258:3  <b>LAH</b> [1] - 1235:14  <b>Lancet</b> [2] - 1177:18,  1177:21  <b>landed</b> [1] - 1177:24  <b>language</b> [13] -  1131:10, 1140:10,  1155:15, 1155:17,  1155:18, 1196:4,  1231:10, 1246:7,  1246:11, 1251:24,  1252:22, 1255:7,  1255:12  <b>Lankford</b> [2] -  1057:21, 1184:8  <b>large</b> [20] - 1031:12,  1045:8, 1045:13,  1045:14, 1045:21,  1046:13, 1048:2,  1065:19, 1117:12,  1117:13, 1119:13,  1139:9, 1146:11,  1146:24, 1147:5,  1151:12, 1151:14,  1186:13, 1219:17,  1219:22  <b>large-scale</b> [2] -  1186:13, 1219:22  <b>largely</b> [6] - 1067:2,  1067:5, 1068:1,  1068:18, 1071:4,  1074:10  <b>largest</b> [3] - 1032:6,  1219:24, 1220:11  <b>last</b> [24] - 1017:1,  1017:3, 1036:14,  1047:9, 1067:7,  1074:6, 1115:17,  1120:14, 1122:25,  1123:1, 1123:2,  1123:8, 1130:13,  1135:6, 1153:19,  1160:20, 1162:8,  1162:9, 1190:23,  1193:10, 1208:22,  1266:23, 1268:11,  1268:23  <b>lastly</b> [2] - 1189:13,  1256:19  <b>late</b> [5] - 1059:5,  1059:7, 1181:1,  1185:3, 1228:1  <b>latest</b> [1] - 1266:17  <b>Latin</b> [2] - 1077:2,  1077:3  <b>law</b> [15] - 1054:12,  1056:5, 1057:4,  1225:23, 1230:22,  1232:3, 1233:2,</p>
<p><b>J</b></p> <p><b>J.C</b> [1] - 1190:19  <b>JACOBS</b> [12] -  1005:12, 1124:17,  1124:24, 1226:5,  1226:10, 1226:16,  1228:14, 1266:6,  1266:18, 1267:15,  1268:22, 1271:10  <b>Jacobs</b> [3] - 1216:23,  1226:3, 1267:1  <b>January</b> [4] - 1173:24,  1180:17, 1182:23,  1217:6  <b>Japan</b> [1] - 1165:4  <b>jet</b> [1] - 1179:16  <b>jobs</b> [1] - 1167:6  <b>JOHN</b> [1] - 1005:3  <b>join</b> [1] - 1068:7  <b>joined</b> [3] - 1017:16,  1231:1, 1255:9  <b>joint</b> [1] - 1265:18  <b>Jonathan</b> [1] -  1215:19  <b>JOSEPHINE</b> [1] -</p>			<p><b>L</b></p> <p><b>lab</b> [1] - 1179:9  <b>label</b> [8] - 1036:21,  1042:7, 1046:2,  1046:22, 1048:22,  1111:3, 1111:4,  1117:8  <b>labeled</b> [1] - 1173:3  <b>labeling</b> [1] - 1046:1  <b>Labeling</b> [1] - 1094:7  <b>laboratory</b> [2] -  1169:21, 1170:16</p>	

<p>1233:5, 1233:7, 1233:12, 1246:6, 1247:18, 1256:2, 1256:3, 1258:18 <b>laws</b> [2] - 1240:20, 1263:20 <b>lawyer</b> [1] - 1087:4 <b>lawyers</b> [6] - 1086:21, 1088:9, 1088:17, 1167:1, 1257:22, 1267:9 <b>lay</b> [1] - 1086:12 <b>lead</b> [2] - 1101:1, 1241:10 <b>leadership</b> [1] - 1027:6 <b>leading</b> [2] - 1046:16, 1261:4 <b>leads</b> [1] - 1268:4 <b>learn</b> [2] - 1064:10, 1084:13 <b>learned</b> [2] - 1012:11, 1063:17 <b>learning</b> [1] - 1016:25 <b>least</b> [22] - 1040:18, 1060:18, 1066:17, 1067:11, 1086:25, 1088:9, 1092:1, 1098:19, 1100:24, 1106:13, 1132:12, 1190:24, 1224:14, 1234:11, 1242:5, 1242:7, 1244:22, 1247:22, 1250:8, 1257:19, 1259:14, 1262:4 <b>leave</b> [5] - 1096:19, 1096:25, 1225:20, 1255:1, 1269:21 <b>leaving</b> [3] - 1112:23, 1226:9, 1247:12 <b>led</b> [1] - 1051:15 <b>leeway</b> [1] - 1125:20 <b>left</b> [24] - 1006:11, 1033:8, 1049:15, 1064:5, 1068:4, 1106:22, 1122:4, 1122:6, 1122:11, 1122:14, 1122:16, 1123:16, 1124:16, 1125:5, 1133:11, 1138:1, 1149:24, 1151:10, 1160:10, 1206:6, 1207:3, 1243:3 <b>left-hand</b> [4] - 1133:11, 1149:24, 1151:10, 1160:10 <b>legal</b> [7] - 1054:12,</p>	<p>1054:18, 1055:14, 1055:25, 1056:10, 1056:13, 1056:17 <b>legitimacy</b> [1] - 1264:18 <b>length</b> [1] - 1268:20 <b>lengthen</b> [1] - 1190:11 <b>lengthens</b> [1] - 1189:23 <b>lengthy</b> [1] - 1235:15 <b>lens</b> [1] - 1056:25 <b>less</b> [6] - 1098:4, 1122:15, 1122:17, 1205:18, 1263:19, 1264:1 <b>lessons</b> [1] - 1118:12 <b>letter</b> [5] - 1031:11, 1031:13, 1249:19, 1251:20, 1263:9 <b>level</b> [6] - 1011:3, 1028:17, 1029:6, 1098:3, 1104:12, 1198:22 <b>levels</b> [8] - 1039:5, 1041:15, 1044:16, 1051:9, 1051:20, 1104:12, 1185:8, 1185:11 <b>leveraged</b> [2] - 1153:1, 1153:9 <b>Lewy</b> [3] - 1173:12, 1204:20, 1218:10 <b>liberal</b> [1] - 1017:22 <b>Library</b> [1] - 1027:22 <b>license</b> [1] - 1010:11 <b>licensed</b> [1] - 1212:11 <b>life</b> [8] - 1037:17, 1040:10, 1040:18, 1040:19, 1105:14, 1175:5, 1175:6, 1246:10 <b>lifetime</b> [1] - 1028:3 <b>light</b> [17] - 1015:24, 1044:21, 1044:22, 1046:14, 1054:14, 1054:15, 1164:13, 1164:15, 1165:16, 1170:9, 1170:23, 1171:3, 1174:24, 1174:25, 1177:14, 1237:18 <b>light/dark</b> [2] - 1170:14, 1170:17 <b>likelihood</b> [1] - 1119:7 <b>likely</b> [8] - 1021:7, 1023:6, 1033:5, 1050:18, 1080:18, 1080:23, 1081:1, 1119:13 <b>limit</b> [5] - 1055:18,</p>	<p>1057:6, 1222:19, 1224:2, 1224:4 <b>limitation</b> [16] - 1223:22, 1224:6, 1228:22, 1232:7, 1232:22, 1234:20, 1236:13, 1238:24, 1243:6, 1248:14, 1255:17, 1255:19, 1255:20, 1255:21, 1257:1 <b>limitations</b> [10] - 1017:13, 1223:10, 1225:24, 1236:7, 1243:17, 1259:8, 1263:23, 1264:1, 1267:24, 1269:15 <b>limited</b> [2] - 1210:5, 1223:18 <b>limiting</b> [1] - 1223:24 <b>limits</b> [1] - 1230:4 <b>line</b> [13] - 1044:18, 1044:21, 1046:15, 1057:5, 1201:5, 1201:11, 1202:11, 1236:10, 1241:23, 1244:10, 1244:19 <b>Line</b> [3] - 1083:19, 1089:25, 1242:14 <b>lines</b> [8] - 1065:7, 1095:9, 1114:19, 1144:8, 1205:4, 1234:14, 1235:18 <b>lining</b> [1] - 1030:18 <b>list</b> [3] - 1015:23, 1130:4, 1265:14 <b>listed</b> [5] - 1129:10, 1141:8, 1220:6, 1220:8, 1220:12 <b>listen</b> [3] - 1125:16, 1224:5, 1225:2 <b>listened</b> [1] - 1188:25 <b>listening</b> [2] - 1187:14, 1227:18 <b>listing</b> [1] - 1042:12 <b>lists</b> [2] - 1042:15, 1069:8 <b>litany</b> [1] - 1187:20 <b>literally</b> [1] - 1017:5 <b>literature</b> [10] - 1034:20, 1038:9, 1042:10, 1072:18, 1104:6, 1105:5, 1106:12, 1109:15, 1117:9, 1181:23 <b>lithium</b> [8] - 1234:11, 1234:23, 1235:8, 1235:14, 1236:5, 1236:17, 1254:16, 1254:17</p>	<p><b>litigation</b> [3] - 1212:21, 1214:5, 1222:17 <b>live</b> [2] - 1084:16, 1253:10 <b>liver</b> [32] - 1030:22, 1031:1, 1031:4, 1031:23, 1032:2, 1032:3, 1033:9, 1034:1, 1034:2, 1034:10, 1039:22, 1041:18, 1051:19, 1053:25, 1061:1, 1061:3, 1061:4, 1065:14, 1065:20, 1075:8, 1075:10, 1076:8, 1076:12, 1077:23, 1078:4, 1080:20, 1081:5, 1081:20, 1082:4, 1083:5, 1146:5, 1150:23 <b>lives</b> [2] - 1178:10, 1187:24 <b>living</b> [5] - 1026:23, 1077:6, 1126:19, 1170:15, 1187:2 <b>LLP</b> [3] - 1005:2, 1005:8, 1005:12 <b>Lockley</b> [3] - 1173:4, 1175:3, 1208:12 <b>logarithmic</b> [1] - 1044:15 <b>London</b> [2] - 1177:23, 1179:17 <b>long-felt</b> [7] - 1187:16, 1217:7, 1222:2, 1223:2, 1223:5, 1224:6, 1224:19 <b>look</b> [69] - 1009:1, 1022:9, 1022:20, 1022:23, 1033:18, 1037:9, 1040:20, 1040:21, 1056:24, 1062:17, 1064:11, 1069:1, 1069:2, 1070:19, 1071:7, 1071:11, 1073:17, 1088:1, 1088:13, 1088:19, 1099:4, 1102:16, 1102:21, 1104:8, 1104:15, 1104:17, 1105:4, 1106:18, 1109:15, 1125:15, 1130:9, 1134:12, 1144:8, 1147:20, 1149:8, 1154:11, 1154:15, 1158:24, 1160:10, 1160:25, 1168:25,</p>	<p>1173:2, 1174:17, 1176:12, 1185:17, 1192:5, 1194:3, 1194:14, 1195:18, 1195:20, 1201:4, 1207:22, 1236:2, 1236:25, 1244:19, 1244:24, 1246:10, 1247:2, 1248:6, 1251:3, 1251:6, 1253:1, 1256:2, 1263:17, 1265:3, 1266:15, 1267:8, 1267:9 <b>looked</b> [9] - 1012:24, 1022:14, 1022:16, 1048:21, 1051:5, 1064:18, 1148:7, 1198:1, 1254:12 <b>looking</b> [23] - 1008:9, 1040:9, 1044:12, 1046:14, 1068:22, 1075:2, 1079:5, 1081:12, 1083:18, 1088:15, 1095:12, 1107:5, 1113:17, 1133:25, 1145:12, 1154:16, 1170:7, 1170:8, 1194:13, 1201:24, 1205:9, 1234:7, 1234:16 <b>looks</b> [2] - 1029:2, 1104:16 <b>lorazepam</b> [1] - 1029:21 <b>lose</b> [1] - 1214:4 <b>lost</b> [1] - 1211:16 <b>low</b> [4] - 1035:17, 1118:6, 1142:2, 1173:18 <b>lower</b> [4] - 1021:21, 1041:21, 1046:15, 1047:25 <b>lowering</b> [1] - 1104:11 <b>lowers</b> [1] - 1189:22 <b>lowest</b> [1] - 1218:10 <b>Lucin</b> [1] - 1252:21 <b>LUKAS</b> [43] - 1023:18, 1025:9, 1025:17, 1025:19, 1026:4, 1026:9, 1028:5, 1028:12, 1032:17, 1032:22, 1034:12, 1034:24, 1035:4, 1035:25, 1036:24, 1037:25, 1038:5, 1038:6, 1038:10, 1038:16, 1038:18, 1043:2, 1044:6, 1044:11, 1045:2,</p>
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1047:10, 1047:12, 1048:21, 1049:2, 1052:3, 1056:19, 1057:10, 1057:25, 1071:22, 1086:11, 1086:14, 1095:22, 1099:14, 1112:25, 1116:5, 1116:7, 1117:14, 1120:21 <b>lunch</b> [3] - 1205:13, 1206:16, 1207:12 <b>luxury</b> [1] - 1165:3 <b>Lynch</b> [4] - 1042:18, 1047:14, 1147:18, 1153:13	<b>manufacture</b> [1] - 1220:25 <b>manufacturer</b> [2] - 1220:19, 1220:22 <b>manufacturers</b> [1] - 1220:24 <b>manufacturing</b> [7] - 1221:7, 1232:23, 1259:22, 1259:25, 1260:11, 1263:2, 1263:10 <b>manuscript</b> [1] - 1106:11 <b>manyfold</b> [1] - 1051:21 <b>map</b> [1] - 1234:20 <b>mapping</b> [2] - 1235:4, 1235:25 <b>maps</b> [1] - 1237:19 <b>marathon</b> [1] - 1202:23 <b>March</b> [2] - 1:16, 1251:21 <b>mark</b> [1] - 1133:16 <b>marked</b> [2] - 1180:9, 1204:7 <b>Markman</b> [4] - 1121:5, 1121:6, 1225:8, 1226:18 <b>mass</b> [4] - 1077:18, 1077:19, 1077:21, 1134:11 <b>Mass</b> [1] - 1026:19 <b>massive</b> [1] - 1116:18 <b>masters</b> [1] - 1253:10 <b>match</b> [1] - 1234:15 <b>material</b> [2] - 1032:13, 1229:8 <b>matter</b> [16] - 1012:21, 1013:1, 1013:6, 1055:25, 1057:6, 1059:10, 1094:18, 1094:19, 1140:3, 1156:24, 1164:7, 1204:16, 1223:8, 1225:23, 1251:16, 1254:7 <b>matters</b> [4] - 1024:16, 1271:7, 1271:12, 1271:21 <b>maximum</b> [2] - 1189:22, 1203:17 <b>mayor</b> [1] - 1160:13 <b>McNeil</b> [2] - 1233:17, 1244:10 <b>MCTIGUE</b> [1] - 1005:16 <b>MD</b> [3] - 1025:13, 1163:18, 1163:22 <b>meal</b> [1] - 1185:25	<b>mean</b> [79] - 1017:7, 1017:11, 1024:11, 1037:17, 1053:3, 1060:17, 1065:19, 1072:18, 1082:14, 1084:5, 1086:16, 1090:24, 1093:11, 1105:1, 1105:6, 1105:8, 1108:23, 1112:5, 1112:17, 1120:25, 1121:13, 1125:8, 1125:15, 1131:20, 1133:18, 1148:25, 1183:2, 1183:12, 1183:19, 1183:22, 1194:11, 1197:24, 1208:17, 1209:2, 1210:1, 1213:4, 1227:19, 1229:16, 1230:9, 1233:12, 1233:14, 1236:23, 1236:24, 1236:25, 1237:16, 1237:25, 1238:1, 1238:5, 1238:11, 1239:7, 1239:10, 1240:5, 1242:13, 1242:23, 1242:24, 1243:1, 1244:12, 1245:4, 1246:8, 1247:1, 1247:4, 1247:13, 1248:8, 1253:18, 1253:20, 1254:11, 1255:11, 1257:7, 1261:7, 1263:13, 1264:5, 1265:17, 1266:16, 1268:4, 1268:16 <b>meaning</b> [27] - 1039:6, 1138:6, 1183:22, 1226:23, 1227:15, 1229:10, 1229:24, 1230:5, 1230:8, 1230:11, 1233:18, 1240:1, 1241:15, 1244:25, 1245:8, 1246:12, 1246:24, 1246:25, 1247:25, 1248:15, 1248:17, 1248:19, 1249:21, 1251:17, 1251:25, 1256:15 <b>meaningful</b> [3] - 1133:21, 1139:16, 1242:21 <b>meaningless</b> [1] - 1245:9 <b>means</b> [27] - 1015:21, 1023:12, 1024:1, 1029:4, 1041:11,	1041:20, 1065:6, 1065:10, 1065:19, 1076:22, 1076:23, 1077:6, 1085:16, 1125:2, 1139:11, 1142:3, 1197:14, 1207:6, 1228:6, 1231:18, 1237:13, 1239:9, 1240:21, 1241:9, 1252:5, 1252:8, 1252:13 <b>meant</b> [9] - 1024:3, 1024:6, 1084:8, 1085:1, 1093:12, 1121:8, 1244:23, 1247:7, 1248:10 <b>measures</b> [1] - 1121:24 <b>mechanically</b> [1] - 1034:4 <b>mechanism</b> [10] - 1035:9, 1035:19, 1037:7, 1037:14, 1040:10, 1048:6, 1104:20, 1109:21, 1110:12, 1110:16 <b>mechanisms</b> [2] - 1026:23, 1040:16 <b>medical</b> [3] - 1063:19, 1186:7, 1219:19 <b>Medical</b> [8] - 1026:14, 1026:16, 1026:17, 1026:20, 1126:21, 1127:24, 1163:11, 1163:17 <b>medication</b> [4] - 1030:2, 1030:11, 1030:12, 1187:19 <b>medications</b> [3] - 1103:12, 1147:22, 1153:23 <b>medicine</b> [6] - 1026:15, 1042:2, 1142:23, 1143:1, 1164:3, 1212:14 <b>Medicine</b> [5] - 1025:22, 1027:22, 1163:11, 1163:12, 1217:19 <b>medium</b> [1] - 1235:23 <b>meet</b> [6] - 1143:8, 1143:24, 1144:12, 1186:6, 1190:21, 1263:6 <b>meeting</b> [9] - 1180:24, 1181:7, 1181:9, 1207:16, 1207:23, 1215:9, 1218:23, 1218:25, 1219:2 <b>meetings</b> [1] - 1174:6	<b>meets</b> [1] - 1263:20 <b>melatonergic</b> [2] - 1069:14, 1107:22 <b>Melatonin</b> [2] - 1072:5, 1159:24 <b>melatonin</b> [83] - 1035:11, 1035:13, 1037:13, 1062:5, 1107:16, 1107:23, 1156:3, 1168:19, 1168:23, 1170:10, 1170:12, 1170:16, 1170:19, 1170:22, 1170:25, 1171:3, 1171:11, 1172:17, 1172:24, 1173:6, 1173:9, 1173:18, 1174:2, 1174:4, 1175:2, 1175:20, 1175:22, 1175:24, 1176:2, 1176:4, 1176:8, 1176:16, 1176:19, 1176:24, 1177:2, 1185:7, 1185:12, 1186:13, 1187:17, 1196:15, 1199:16, 1200:5, 1200:7, 1201:16, 1203:3, 1204:18, 1208:10, 1208:14, 1208:16, 1208:17, 1208:23, 1208:24, 1209:1, 1209:20, 1209:21, 1210:2, 1210:12, 1210:16, 1210:21, 1211:13, 1211:20, 1214:17, 1214:19, 1214:21, 1217:14, 1217:15, 1218:2, 1218:24, 1219:5, 1219:6, 1220:8, 1220:12, 1220:19, 1221:6, 1221:10, 1224:10 <b>melting</b> [2] - 1021:20, 1264:7 <b>member</b> [4] - 1027:15, 1027:17, 1029:9, 1029:14 <b>members</b> [1] - 1185:1 <b>membrane</b> [1] - 1034:6 <b>membrane-bound</b> [1] - 1034:6 <b>Memorial</b> [2] - 1267:13, 1267:20 <b>mention</b> [6] - 1055:7, 1070:17, 1155:20, 1191:8, 1192:7, 1198:2
<b>M</b>				
<b>M.D</b> [1] - 1142:25 <b>M11</b> [1] - 1161:5 <b>M12</b> [1] - 1161:5 <b>M13</b> [1] - 1161:5 <b>M14</b> [1] - 1161:5 <b>M9</b> [1] - 1161:5 <b>magnitude</b> [17] - 1051:23, 1086:1, 1086:4, 1089:8, 1090:3, 1090:6, 1090:23, 1090:24, 1091:16, 1092:13, 1155:9, 1155:13, 1155:15, 1155:21, 1155:23, 1155:25 <b>magnitudes</b> [1] - 1172:20 <b>main</b> [3] - 1072:21, 1073:1, 1174:20 <b>mainstream</b> [1] - 1252:18 <b>maintain</b> [3] - 1166:6, 1166:19, 1179:6 <b>maintained</b> [1] - 1178:4 <b>maintaining</b> [1] - 1196:13 <b>maintenance</b> [2] - 1203:6, 1203:19 <b>major</b> [7] - 1041:24, 1116:19, 1127:10, 1131:25, 1133:1, 1136:24, 1161:2 <b>majority</b> [1] - 1148:17 <b>mammals</b> [1] - 1202:21 <b>management</b> [1] - 1057:6 <b>manipulations</b> [1] - 1235:16 <b>mannerism</b> [1] - 1258:2				

<p><b>mentioned</b> <sup>[16]</sup> - 1016:25, 1017:21, 1036:14, 1045:10, 1063:13, 1064:25, 1117:25, 1151:19, 1151:23, 1154:13, 1165:22, 1185:15, 1186:10, 1199:1, 1264:21, 1264:24</p> <p><b>mentions</b> <sup>[1]</sup> - 1154:2</p> <p><b>mere</b> <sup>[1]</sup> - 1155:23</p> <p><b>merely</b> <sup>[1]</sup> - 1078:25</p> <p><b>message</b> <sup>[1]</sup> - 1047:17</p> <p><b>met</b> <sup>[4]</sup> - 1017:13, 1052:10, 1190:20, 1263:24</p> <p><b>meta</b> <sup>[3]</sup> - 1218:4, 1218:7</p> <p><b>meta-analysis</b> <sup>[3]</sup> - 1218:4, 1218:7</p> <p><b>metabolic</b> <sup>[7]</sup> - 1039:3, 1042:13, 1048:7, 1115:20, 1132:14, 1133:8, 1145:23</p> <p><b>metabolism</b> <sup>[72]</sup> - 1028:7, 1028:19, 1029:11, 1030:7, 1030:17, 1030:23, 1031:6, 1031:19, 1031:22, 1031:25, 1033:5, 1033:17, 1036:4, 1039:1, 1039:7, 1039:22, 1040:12, 1041:2, 1041:5, 1041:7, 1041:13, 1041:21, 1048:7, 1049:20, 1051:8, 1055:3, 1064:10, 1064:11, 1069:14, 1070:18, 1073:10, 1074:4, 1074:9, 1074:12, 1075:3, 1076:12, 1076:17, 1077:17, 1078:1, 1078:18, 1080:18, 1081:2, 1081:17, 1082:7, 1092:4, 1092:10, 1096:10, 1103:22, 1104:1, 1104:11, 1104:22, 1108:20, 1109:3, 1109:11, 1112:6, 1112:7, 1114:18, 1130:8, 1132:6, 1135:12, 1136:7, 1136:21, 1136:24, 1138:7, 1141:23, 1142:8, 1146:11, 1147:22,</p>	<p>1160:13, 1161:3, 1161:15, 1185:4</p> <p><b>Metabolism</b> <sup>[6]</sup> - 1039:21, 1064:6, 1072:4, 1115:9, 1115:14, 1150:22</p> <p><b>metabolisms</b> <sup>[1]</sup> - 1126:25</p> <p><b>metabolite</b> <sup>[4]</sup> - 1078:16, 1078:18, 1079:1, 1079:15</p> <p><b>metabolites</b> <sup>[14]</sup> - 1033:5, 1077:25, 1078:22, 1079:6, 1080:23, 1134:13, 1135:6, 1135:8, 1135:9, 1135:15, 1135:19, 1138:4, 1138:8, 1161:5</p> <p><b>metabolize</b> <sup>[16]</sup> - 1041:12, 1041:20, 1066:18, 1078:21, 1114:25, 1115:24, 1131:3, 1131:16, 1131:23, 1140:24, 1141:13, 1146:15, 1146:22, 1147:1, 1147:10, 1148:1</p> <p><b>metabolized</b> <sup>[34]</sup> - 1036:8, 1066:7, 1066:19, 1067:25, 1069:17, 1073:25, 1074:24, 1075:6, 1075:7, 1075:10, 1075:11, 1075:17, 1076:13, 1077:23, 1079:14, 1092:20, 1100:8, 1100:10, 1100:21, 1101:10, 1103:7, 1103:17, 1104:6, 1105:3, 1114:21, 1115:22, 1116:10, 1135:23, 1139:15, 1140:15, 1141:7, 1156:3, 1156:8</p> <p><b>metabolizes</b> <sup>[3]</sup> - 1032:4, 1078:25, 1140:22</p> <p><b>metabolizing</b> <sup>[5]</sup> - 1031:3, 1040:22, 1133:7, 1142:4, 1159:4</p> <p><b>methanamine</b> <sup>[4]</sup> - 1006:25, 1007:8, 1007:12, 1251:11</p> <p><b>method</b> <sup>[13]</sup> - 1008:8, 1192:1, 1192:2, 1195:23, 1195:24, 1196:5, 1196:6,</p>	<p>1196:7, 1196:14, 1197:15, 1222:12, 1258:14, 1259:11</p> <p><b>methodologies</b> <sup>[1]</sup> - 1083:25</p> <p><b>methodology</b> <sup>[1]</sup> - 1083:20</p> <p><b>methods</b> <sup>[1]</sup> - 1258:24</p> <p><b>mic</b> <sup>[1]</sup> - 1089:3</p> <p><b>Michele</b> <sup>[2]</sup> - 2:1, 1272:7</p> <p><b>micromolar</b> <sup>[1]</sup> - 1035:24</p> <p><b>microorganism</b> <sup>[1]</sup> - 1065:24</p> <p><b>microorganisms</b> <sup>[2]</sup> - 1033:12, 1065:13</p> <p><b>microphone</b> <sup>[1]</sup> - 1187:1</p> <p><b>microsome</b> <sup>[2]</sup> - 1034:1, 1081:20</p> <p><b>microsomes</b> <sup>[15]</sup> - 1034:6, 1034:8, 1039:22, 1064:21, 1065:5, 1065:23, 1067:24, 1068:5, 1068:6, 1073:21, 1081:5, 1083:6, 1085:14, 1136:22, 1150:23</p> <p><b>mid</b> <sup>[1]</sup> - 1079:23</p> <p><b>mid-morning</b> <sup>[1]</sup> - 1079:23</p> <p><b>midazolam</b> <sup>[1]</sup> - 1029:22</p> <p><b>middle</b> <sup>[1]</sup> - 1231:25</p> <p><b>midnight</b> <sup>[1]</sup> - 1185:10</p> <p><b>might</b> <sup>[34]</sup> - 1011:24, 1011:25, 1019:10, 1022:1, 1054:24, 1064:10, 1078:8, 1094:18, 1101:11, 1101:17, 1102:2, 1113:7, 1118:16, 1119:2, 1119:12, 1120:24, 1135:12, 1146:24, 1182:1, 1200:17, 1201:17, 1205:11, 1205:18, 1211:1, 1227:19, 1229:1, 1230:14, 1237:10, 1244:16, 1249:7, 1252:2, 1268:16, 1270:24</p> <p><b>mild</b> <sup>[1]</sup> - 1085:22</p> <p><b>milligrams</b> <sup>[13]</sup> - 1173:12, 1173:14, 1176:19, 1177:2, 1178:6, 1178:7, 1178:9, 1178:19,</p>	<p>1180:13, 1196:15, 1196:25, 1197:7, 1211:2</p> <p><b>MILLIKEN</b> <sup>[10]</sup> - 1005:5, 1215:18, 1215:25, 1216:7, 1216:11, 1216:25, 1219:8, 1219:14, 1220:15, 1221:16</p> <p><b>million</b> <sup>[2]</sup> - 1214:2, 1219:18</p> <p><b>mind</b> <sup>[8]</sup> - 1056:3, 1058:23, 1068:11, 1082:21, 1122:12, 1192:16, 1239:18, 1258:6</p> <p><b>minor</b> <sup>[2]</sup> - 1131:25, 1161:3</p> <p><b>minus</b> <sup>[3]</sup> - 1021:23, 1021:24, 1230:14</p> <p><b>minute</b> <sup>[5]</sup> - 1064:20, 1075:5, 1125:4, 1125:11, 1192:22</p> <p><b>minutes</b> <sup>[29]</sup> - 1017:4, 1019:11, 1019:13, 1079:25, 1122:4, 1122:16, 1123:12, 1123:19, 1123:24, 1124:11, 1124:12, 1124:13, 1124:15, 1125:1, 1125:6, 1125:21, 1125:23, 1176:9, 1176:10, 1176:17, 1177:2, 1177:9, 1177:20, 1205:12, 1205:19, 1206:7, 1207:4, 1207:8, 1210:9</p> <p><b>misaligned</b> <sup>[1]</sup> - 1183:24</p> <p><b>misheard</b> <sup>[2]</sup> - 1105:17, 1130:17</p> <p><b>missed</b> <sup>[1]</sup> - 1084:22</p> <p><b>misspoke</b> <sup>[4]</sup> - 1014:5, 1024:4, 1067:16, 1176:24</p> <p><b>mistake</b> <sup>[1]</sup> - 1175:19</p> <p><b>misunderstood</b> <sup>[1]</sup> - 1248:9</p> <p><b>mixing</b> <sup>[2]</sup> - 1248:16, 1248:17</p> <p><b>model</b> <sup>[3]</sup> - 1033:13, 1202:3, 1220:23</p> <p><b>models</b> <sup>[3]</sup> - 1033:2, 1039:12, 1040:18</p> <p><b>moderate</b> <sup>[1]</sup> - 1161:17</p> <p><b>modified</b> <sup>[4]</sup> - 1230:14, 1231:8, 1250:6, 1250:19</p>	<p><b>modifier</b> <sup>[1]</sup> - 1089:17</p> <p><b>modifies</b> <sup>[1]</sup> - 1041:7</p> <p><b>modifying</b> <sup>[1]</sup> - 1240:10</p> <p><b>mold</b> <sup>[1]</sup> - 1154:24</p> <p><b>molecular</b> <sup>[2]</sup> - 1035:18, 1163:15</p> <p><b>molecule</b> <sup>[6]</sup> - 1078:14, 1105:3, 1146:21, 1147:11, 1233:20, 1243:14</p> <p><b>molecules</b> <sup>[3]</sup> - 1108:16, 1146:14, 1148:17</p> <p><b>Moltke</b> <sup>[1]</sup> - 1044:1</p> <p><b>moment</b> <sup>[18]</sup> - 1008:3, 1027:7, 1038:2, 1052:5, 1058:17, 1065:2, 1065:4, 1066:9, 1082:25, 1088:13, 1096:19, 1098:2, 1100:2, 1101:7, 1102:5, 1102:8, 1188:8, 1206:12</p> <p><b>monitoring</b> <sup>[1]</sup> - 1091:13</p> <p><b>Montefiore</b> <sup>[1]</sup> - 1026:15</p> <p><b>month</b> <sup>[8]</sup> - 1059:6, 1059:12, 1194:6, 1213:8, 1213:9, 1213:10, 1266:23, 1267:14</p> <p><b>monthly</b> <sup>[1]</sup> - 1213:7</p> <p><b>months</b> <sup>[1]</sup> - 1265:25</p> <p><b>morning</b> <sup>[16]</sup> - 1006:5, 1006:9, 1006:10, 1018:8, 1023:18, 1025:10, 1025:11, 1025:15, 1028:15, 1068:9, 1079:23, 1167:15, 1168:3, 1168:9, 1188:19, 1218:20</p> <p><b>MORRIS</b> <sup>[1]</sup> - 1005:12</p> <p><b>most</b> <sup>[22]</sup> - 1028:1, 1030:15, 1031:4, 1031:22, 1031:24, 1032:6, 1051:18, 1102:1, 1119:14, 1134:14, 1142:6, 1148:2, 1161:4, 1167:24, 1170:17, 1171:3, 1183:7, 1200:22, 1202:21, 1213:13, 1214:20, 1258:24</p> <p><b>mostly</b> <sup>[3]</sup> - 1040:11, 1070:20, 1228:7</p>
--	---	--	--	---



<b>motion</b> <sup>[5]</sup> - 1014:14, 1221:22, 1225:13, 1226:6, 1226:11	1052:3, 1052:4, 1052:8, 1054:7, 1054:13, 1054:19, 1055:15, 1056:2, 1056:16, 1056:19, 1057:9, 1057:10, 1057:14, 1057:25, 1058:2, 1058:7, 1058:12, 1058:16, 1061:16, 1061:18, 1063:24, 1064:1, 1064:15, 1064:17, 1069:4, 1069:6, 1071:21, 1071:22, 1071:25, 1072:2, 1073:14, 1073:16, 1073:18, 1073:20, 1079:17, 1079:24, 1080:8, 1080:13, 1086:11, 1086:13, 1086:14, 1086:15, 1086:19, 1086:23, 1087:2, 1087:14, 1087:21, 1088:5, 1088:11, 1089:1, 1089:5, 1089:6, 1089:23, 1094:25, 1095:2, 1095:8, 1095:11, 1095:17, 1095:22, 1095:25, 1096:1, 1096:18, 1096:21, 1099:7, 1099:9, 1099:13, 1099:14, 1099:17, 1099:20, 1099:21, 1106:19, 1106:21, 1107:9, 1107:11, 1110:20, 1110:23, 1110:25, 1111:1, 1112:17, 1112:22, 1112:25, 1113:12, 1113:16, 1114:13, 1114:16, 1116:2, 1116:5, 1116:7, 1117:14, 1120:9, 1120:18, 1120:21, 1120:24, 1121:3, 1121:8, 1121:12, 1122:5, 1122:8, 1122:13, 1122:21, 1123:2, 1123:7, 1123:11, 1123:15, 1123:19, 1123:23, 1124:7, 1124:15, 1125:11, 1125:19, 1126:2, 1126:5, 1126:15, 1127:16, 1127:18, 1127:21, 1128:21, 1128:24, 1129:1, 1129:6, 1129:7, 1129:22,	1129:24, 1130:16, 1130:21, 1130:23, 1132:20, 1132:22, 1134:22, 1134:24, 1136:10, 1136:12, 1136:15, 1137:8, 1137:10, 1137:13, 1137:20, 1137:22, 1139:3, 1139:19, 1139:22, 1140:1, 1140:4, 1140:6, 1140:17, 1140:19, 1141:2, 1141:4, 1142:13, 1142:17, 1142:19, 1147:15, 1147:16, 1150:15, 1150:16, 1151:3, 1151:5, 1151:8, 1155:2, 1155:6, 1156:11, 1156:13, 1156:23, 1157:1, 1157:2, 1157:5, 1157:10, 1157:14, 1158:11, 1158:14, 1158:19, 1159:16, 1159:19, 1161:22, 1161:24, 1162:1, 1162:3, 1162:19, 1162:24, 1163:3, 1163:5, 1165:9, 1165:15, 1166:10, 1166:15, 1169:9, 1169:11, 1169:14, 1169:25, 1170:1, 1170:4, 1170:6, 1171:22, 1171:24, 1172:4, 1172:6, 1172:8, 1180:5, 1185:19, 1185:21, 1186:1, 1190:14, 1190:18, 1191:20, 1191:24, 1205:10, 1205:14, 1205:18, 1205:22, 1206:1, 1206:3, 1206:4, 1206:7, 1206:9, 1206:12, 1206:17, 1206:21, 1206:24, 1207:9, 1207:14, 1207:24, 1208:1, 1209:4, 1209:7, 1209:13, 1209:15, 1209:18, 1210:11, 1211:19, 1214:10, 1214:14, 1214:24, 1215:15, 1215:18, 1215:25, 1216:7, 1216:11, 1216:13, 1216:25, 1219:8, 1219:11, 1219:14, 1220:15, 1221:12,	1221:16, 1221:18, 1221:21, 1222:3, 1222:5, 1222:8, 1222:14, 1222:16, 1222:20, 1222:24, 1223:3, 1223:13, 1224:8, 1224:21, 1225:4, 1225:7, 1225:12, 1225:16, 1225:22, 1226:3, 1226:20, 1227:3, 1227:5, 1227:8, 1227:11, 1227:14, 1227:22, 1227:24, 1228:3, 1228:8, 1228:17, 1228:20, 1229:13, 1229:18, 1230:7, 1230:16, 1230:21, 1231:17, 1232:13, 1233:15, 1234:1, 1235:11, 1235:13, 1236:12, 1236:23, 1237:2, 1237:6, 1237:24, 1238:10, 1238:16, 1238:21, 1239:2, 1239:12, 1239:17, 1239:23, 1240:8, 1240:14, 1240:15, 1240:18, 1241:19, 1241:20, 1242:1, 1242:5, 1242:9, 1242:12, 1242:18, 1243:9, 1243:20, 1244:2, 1244:6, 1244:8, 1244:14, 1245:4, 1245:21, 1245:24, 1246:3, 1246:5, 1246:14, 1246:17, 1246:21, 1247:1, 1247:7, 1248:2, 1248:5, 1248:9, 1248:24, 1249:5, 1249:9, 1249:10, 1249:16, 1250:4, 1250:8, 1250:12, 1250:15, 1250:20, 1250:24, 1253:14, 1253:17, 1253:21, 1253:23, 1254:3, 1254:6, 1254:10, 1254:19, 1257:5, 1257:13, 1257:20, 1258:17, 1258:21, 1258:25, 1259:13, 1260:2, 1260:14, 1260:15, 1260:22, 1261:3, 1261:8, 1261:17, 1261:20, 1261:23, 1262:2, 1262:10,	1262:20, 1262:23, 1263:16, 1264:3, 1264:5, 1264:10, 1264:20, 1264:25, 1265:13, 1265:20, 1266:1, 1266:7, 1266:11, 1266:14, 1267:7, 1268:3, 1268:8, 1270:10, 1270:21, 1270:23, 1271:5, 1271:15 <b>MS</b> <sup>[19]</sup> - 1014:3, 1019:17, 1019:19, 1019:25, 1020:6, 1021:1, 1023:7, 1037:4, 1124:17, 1124:24, 1226:5, 1226:10, 1226:16, 1228:14, 1266:6, 1266:18, 1267:15, 1268:22, 1271:10 <b>MT-1</b> <sup>[8]</sup> - 1035:13, 1040:17, 1107:13, 1107:21, 1108:2, 1110:6, 1157:23, 1210:3 <b>MT-2</b> <sup>[8]</sup> - 1035:14, 1040:17, 1107:13, 1107:21, 1108:2, 1110:6, 1157:23, 1210:3 <b>multiple</b> <sup>[3]</sup> - 1178:15, 1187:18, 1242:8 <b>must</b> <sup>[7]</sup> - 1024:23, 1025
---	--	---	--	--

<p>1056:21, 1073:4  <b>narrows</b> [1] - 1031:14  <b>NATHAN</b> [1] - 1005:3  <b>National</b> [1] - 1027:22  <b>natural</b> [1] - 1084:15  <b>nature</b> [4] - 1015:3,  1019:9, 1104:24,  1159:8  <b>NDA</b> [1] - 1106:8  <b>near</b> [6] - 1156:24,  1170:23, 1196:9,  1199:25, 1202:5,  1211:2  <b>necessarily</b> [8] -  1017:11, 1017:13,  1022:18, 1100:25,  1177:5, 1200:16,  1228:4, 1235:16  <b>necessary</b> [6] -  1050:16, 1051:22,  1198:23, 1240:20,  1244:5, 1255:22  <b>need</b> [69] - 1011:23,  1012:7, 1012:13,  1013:8, 1042:4,  1047:19, 1052:1,  1054:2, 1071:1,  1077:8, 1081:20,  1081:22, 1081:25,  1083:24, 1084:3,  1085:5, 1085:8,  1085:17, 1085:19,  1086:2, 1086:4,  1089:8, 1090:11,  1090:12, 1090:14,  1090:16, 1091:22,  1100:11, 1119:18,  1123:12, 1124:8,  1132:12, 1132:15,  1134:9, 1143:8,  1143:24, 1144:12,  1144:21, 1162:1,  1166:21, 1183:8,  1186:7, 1187:16,  1194:17, 1195:1,  1197:13, 1205:20,  1206:15, 1217:7,  1223:5, 1224:6,  1224:19, 1226:19,  1228:12, 1249:24,  1250:24, 1250:25,  1252:13, 1252:19,  1257:3, 1265:24,  1266:4, 1266:16,  1266:17, 1266:19,  1266:20, 1269:9,  1269:18, 1270:8  <b>needed</b> [8] - 1010:11,  1050:19, 1096:22,  1098:5, 1098:12,</p>	<p>1101:19, 1117:7,  1135:1  <b>needlessly</b> [1] -  1102:3  <b>needs</b> [6] - 1042:7,  1047:22, 1053:4,  1196:21, 1223:2,  1250:21  <b>negatives</b> [1] -  1216:21  <b>neglected</b> [1] - 1209:5  <b>negligible</b> [1] - 1132:5  <b>neighborhood</b> [1] -  1146:25  <b>net</b> [2] - 1175:18,  1177:15  <b>neurobiology</b> [2] -  1163:24, 1167:9  <b>neurosciences</b> [1] -  1163:17  <b>never</b> [9] - 1054:4,  1070:8, 1094:14,  1094:21, 1105:16,  1142:23, 1162:11,  1212:11, 1237:14  <b>new</b> [18] - 1009:20,  1009:23, 1010:2,  1010:3, 1091:8,  1118:21, 1145:13,  1150:4, 1150:10,  1152:25, 1153:8,  1159:2, 1170:22,  1173:21, 1179:15,  1258:21, 1259:2,  1267:5  <b>New</b> [3] - 1054:22,  1165:20, 1173:11  <b>newly</b> [1] - 1179:15  <b>next</b> [27] - 1035:22,  1035:23, 1076:16,  1076:25, 1094:4,  1097:5, 1099:4,  1115:6, 1115:19,  1120:18, 1123:5,  1150:10, 1162:18,  1162:19, 1171:12,  1172:6, 1175:20,  1175:22, 1177:7,  1178:3, 1181:11,  1199:12, 1259:6,  1265:25, 1269:15,  1271:4  <b>nexus</b> [5] - 1223:1,  1223:9, 1223:14,  1224:6, 1224:11  <b>nicely</b> [1] - 1141:15  <b>NICHOLAS</b> [1] -  1005:8  <b>NICHOLS</b> [1] -  1005:12</p>	<p><b>night</b> [8] - 1017:1,  1165:3, 1165:6,  1166:21, 1166:22,  1167:5, 1185:8,  1187:6  <b>nighttime</b> [1] -  1164:21  <b>NIH</b> [1] - 1034:3  <b>nitrogen</b> [1] - 1157:16  <b>NO</b> [1] - 1:6  <b>nobody's</b> [1] -  1059:17  <b>noise</b> [1] - 1187:7  <b>nomenclature</b> [1] -  1031:10  <b>Non-24</b> [52] - 1057:17,  1110:1, 1163:2,  1167:9, 1168:14,  1174:2, 1186:6,  1186:22, 1190:22,  1191:8, 1192:10,  1192:15, 1194:17,  1195:3, 1196:8,  1198:3, 1199:24,  1200:1, 1200:22,  1201:23, 1202:4,  1207:20, 1209:22,  1210:13, 1210:16,  1210:20, 1210:21,  1211:8, 1212:1,  1212:5, 1212:16,  1214:17, 1217:8,  1217:17, 1217:22,  1218:1, 1218:8,  1218:17, 1218:23,  1219:6, 1220:2,  1220:7, 1220:10,  1220:13, 1222:7,  1222:13, 1222:23,  1223:5, 1223:16,  1223:19, 1224:13  <b>non-24</b> [2] - 1057:19,  1059:23  <b>Non-24-hour</b> [4] -  1164:17, 1186:11,  1192:4, 1192:8  <b>nonbinding</b> [1] -  1143:13  <b>none</b> [3] - 1022:12,  1155:7, 1155:19  <b>nonetheless</b> [2] -  1164:22, 1265:2  <b>noninfringement</b> [4] -  1221:24, 1266:5,  1268:4, 1269:12  <b>nonobvious</b> [2] -  1258:22, 1259:3  <b>nonoxidizing</b> [1] -  1237:10  <b>nonworking</b> [1] -</p>	<p>1241:11  <b>normal</b> [2] - 1167:12,  1167:18  <b>normally</b> [2] -  1065:21, 1270:13  <b>notation</b> [2] - 1234:7,  1234:17  <b>notations</b> [1] -  1234:18  <b>NOTE</b> [1] - 1006:3  <b>note</b> [2] - 1022:16,  1216:2  <b>noted</b> [1] - 1046:22  <b>notes</b> [1] - 1272:5  <b>nothing</b> [7] - 1022:7,  1022:15, 1109:14,  1161:22, 1222:11,  1241:7, 1259:9  <b>notice</b> [2] - 1044:15,  1172:12  <b>noticed</b> [2] - 1023:21,  1176:7  <b>notwithstanding</b> [4] -  1104:23, 1105:1,  1105:7, 1105:8  <b>noun</b> [1] - 1078:18  <b>Novel</b> [2] - 1072:4,  1159:24  <b>novel</b> [1] - 1259:11  <b>November</b> [1] - 1162:9  <b>nowhere</b> [1] - 1110:20  <b>nuanced</b> [1] - 1246:16  <b>nucleus</b> [1] - 1107:17  <b>nullified</b> [1] - 1246:20  <b>nullifies</b> [1] - 1256:11  <b>number</b> [24] -  1027:15, 1027:17,  1029:20, 1030:4,  1031:11, 1031:12,  1031:15, 1036:14,  1052:19, 1057:7,  1068:1, 1082:23,  1096:12, 1111:4,  1139:9, 1146:11,  1146:24, 1151:12,  1156:21, 1157:19,  1157:21, 1160:17,  1235:17  <b>numbering</b> [1] -  1027:21  <b>numbers</b> [7] -  1035:14, 1035:15,  1035:17, 1108:4,  1111:18, 1115:11,  1199:9  <b>numerous</b> [4] -  1042:12, 1043:7,  1242:15, 1262:15</p>	<p><b>O</b>  <b>o'clock</b> [3] - 1019:14,  1168:2, 1172:18  <b>O'CONNOR</b> [1] -  1005:15  <b>oath</b> [7] - 1006:6,  1020:3, 1020:4,  1087:12, 1126:13,  1193:2, 1215:24  <b>obach</b> [1] - 1150:19  <b>Obach</b> [3] - 1039:20,  1039:24, 1040:3  <b>Obahi</b> [1] - 1056:20  <b>object</b> [1] - 1028:9  <b>objection</b> [35] -  1014:9, 1016:2,  1020:22, 1026:6,  1028:10, 1032:19,  1035:1, 1037:1,  1038:3, 1038:12,  1042:24, 1044:8,  1048:24, 1071:22,  1086:11, 1095:22,  1099:14, 1127:18,  1128:24, 1136:12,  1137:10, 1139:22,  1151:5, 1156:23,  1158:3, 1158:6,  1162:3, 1163:3,  1169:11, 1170:1,  1171:24, 1185:21,  1209:15, 1219:10,  1219:11  <b>objects</b> [2] - 1231:1,  1255:9  <b>obligatory</b> [1] -  1110:14  <b>observation</b> [1] -  1050:5  <b>observed</b> [5] - 1074:5,  1074:12, 1075:3,  1175:16  <b>obtain</b> [1] - 1263:13  <b>obtained</b> [2] - 1022:8,  1139:10  <b>obtaining</b> [1] -  1013:12  <b>obvious</b> [16] - 1048:5,  1048:8, 1048:13,  1050:13, 1050:17,  1051:25, 1054:23,  1057:2, 1061:10,  1180:17, 1180:20,  1188:24, 1189:7,  1189:11, 1189:12,  1200:16  <b>obviously</b> [5] -  1015:1, 1116:24,  1124:18, 1184:13,</p>
---	--	--	---	--

<p>1257:21</p> <p><b>obviousness</b> <sup>[14]</sup> - 1028:20, 1048:11, 1049:5, 1050:11, 1052:21, 1053:5, 1054:13, 1055:12, 1059:3, 1061:11, 1072:22, 1073:4, 1198:9, 1198:24</p> <p><b>occasion</b> <sup>[4]</sup> - 1087:6, 1087:10, 1089:16, 1193:10</p> <p><b>occupation</b> <sup>[1]</sup> - 1025:20</p> <p><b>occupational</b> <sup>[1]</sup> - 1164:2</p> <p><b>occupied</b> <sup>[1]</sup> - 1025:21</p> <p><b>occur</b> <sup>[3]</sup> - 1080:18, 1133:10, 1255:14</p> <p><b>occurred</b> <sup>[1]</sup> - 1227:17</p> <p><b>occurring</b> <sup>[2]</sup> - 1167:13, 1183:25</p> <p><b>occurs</b> <sup>[1]</sup> - 1259:7</p> <p><b>October</b> <sup>[11]</sup> - 1145:18, 1145:22, 1146:3, 1146:14, 1146:20, 1147:8, 1148:18, 1148:23, 1149:3, 1156:2, 1156:7</p> <p><b>OF</b> <sup>[1]</sup> - 1:3</p> <p><b>offer</b> <sup>[15]</sup> - 1014:7, 1028:5, 1071:21, 1095:21, 1099:13, 1127:16, 1128:21, 1136:10, 1137:8, 1139:21, 1151:3, 1162:2, 1169:9, 1169:25, 1171:22</p> <p><b>offered</b> <sup>[3]</sup> - 1095:19, 1126:25, 1139:19</p> <p><b>offering</b> <sup>[1]</sup> - 1109:24</p> <p><b>offers</b> <sup>[1]</sup> - 1185:19</p> <p><b>office</b> <sup>[2]</sup> - 1014:8, 1265:1</p> <p><b>often</b> <sup>[7]</sup> - 1166:20, 1167:2, 1224:1, 1232:24, 1259:1, 1262:6, 1270:13</p> <p><b>Ogilvie</b> <sup>[1]</sup> - 1159:20</p> <p><b>Ogu</b> <sup>[2]</sup> - 1042:16, 1047:14</p> <p><b>old</b> <sup>[2]</sup> - 1009:9, 1010:3</p> <p><b>omitted</b> <sup>[2]</sup> - 1157:24, 1188:14</p> <p><b>omitting</b> <sup>[1]</sup> - 1234:25</p> <p><b>once</b> <sup>[12]</sup> - 1012:24, 1120:4, 1185:12,</p>	<p>1193:9, 1196:16, 1196:25, 1197:7, 1239:7, 1240:16, 1242:10, 1250:6, 1255:24</p> <p><b>one</b> <sup>[185]</sup> - 1011:19, 1014:4, 1014:5, 1016:24, 1017:19, 1021:5, 1021:11, 1021:23, 1022:1, 1022:21, 1023:4, 1026:15, 1026:16, 1027:7, 1031:17, 1032:1, 1038:2, 1041:5, 1041:11, 1052:4, 1053:1, 1053:23, 1054:24, 1055:19, 1055:20, 1057:14, 1058:4, 1060:1, 1064:24, 1065:18, 1065:22, 1066:20, 1067:6, 1067:7, 1068:2, 1069:19, 1070:21, 1072:20, 1072:21, 1072:25, 1075:2, 1075:15, 1076:9, 1077:16, 1078:8, 1081:5, 1082:9, 1083:20, 1084:13, 1084:20, 1085:8, 1085:22, 1091:5, 1091:11, 1091:12, 1092:19, 1097:1, 1098:20, 1103:9, 1105:12, 1105:21, 1106:14, 1109:3, 1113:7, 1118:18, 1121:14, 1122:25, 1123:2, 1127:10, 1129:11, 1129:13, 1130:2, 1131:13, 1131:24, 1131:25, 1132:13, 1136:6, 1136:23, 1138:17, 1139:5, 1139:13, 1145:23, 1151:20, 1151:22, 1152:3, 1153:19, 1157:16, 1160:25, 1161:24, 1164:11, 1164:16, 1166:14, 1169:5, 1172:18, 1173:2, 1173:5, 1175:21, 1177:17, 1177:18, 1178:20, 1179:1, 1179:2, 1179:23, 1180:14, 1181:4, 1181:25, 1184:2, 1184:25, 1185:16, 1185:24, 1186:16,</p>	<p>1186:25, 1187:8, 1187:9, 1188:1, 1188:13, 1191:3, 1191:11, 1195:1, 1196:1, 1196:20, 1199:12, 1204:16, 1204:17, 1208:19, 1210:23, 1211:1, 1213:4, 1214:2, 1214:15, 1216:18, 1216:20, 1216:21, 1220:12, 1220:21, 1222:1, 1222:18, 1223:14, 1224:14, 1225:1, 1225:15, 1228:12, 1231:5, 1232:25, 1233:17, 1234:15, 1236:18, 1238:10, 1240:10, 1240:21, 1242:5, 1242:7, 1242:19, 1243:2, 1243:18, 1246:12, 1247:4, 1247:22, 1249:3, 1251:14, 1252:19, 1253:4, 1254:13, 1254:19, 1258:10, 1259:1, 1262:6, 1262:25, 1263:6, 1263:24, 1264:2, 1266:24, 1268:1, 1269:13, 1270:15, 1270:16, 1271:15, 1271:17</p> <p><b>one's</b> <sup>[1]</sup> - 1109:5</p> <p><b>one-fifth</b> <sup>[1]</sup> - 1181:4</p> <p><b>one-to-one</b> <sup>[1]</sup> - 1234:15</p> <p><b>ones</b> <sup>[3]</sup> - 1031:4, 1031:21, 1214:17</p> <p><b>online</b> <sup>[1]</sup> - 1221:10</p> <p><b>onset</b> <sup>[3]</sup> - 1175:25, 1176:1, 1180:21</p> <p><b>open</b> <sup>[1]</sup> - 1120:15</p> <p><b>opening</b> <sup>[2]</sup> - 1269:10</p> <p><b>operations</b> <sup>[2]</sup> - 1234:4, 1235:18</p> <p><b>opiates</b> <sup>[1]</sup> - 1074:20</p> <p><b>opinion</b> <sup>[34]</sup> - 1012:8, 1012:13, 1013:7, 1021:18, 1024:16, 1049:11, 1050:7, 1050:11, 1051:3, 1051:22, 1055:14, 1062:9, 1098:25, 1101:6, 1101:24, 1104:2, 1109:24, 1116:13, 1129:17, 1141:8, 1174:1, 1174:3, 1180:16,</p>	<p>1184:11, 1186:4, 1188:22, 1189:10, 1214:18, 1217:7, 1217:10, 1217:12, 1217:13, 1224:19, 1264:17</p> <p><b>Opinion</b> <sup>[1]</sup> - 1061:20</p> <p><b>opinions</b> <sup>[20]</sup> - 1011:17, 1011:19, 1012:4, 1025:23, 1029:6, 1032:13, 1034:22, 1037:23, 1040:4, 1043:22, 1055:11, 1072:22, 1136:8, 1137:6, 1165:25, 1166:2, 1169:23, 1171:20, 1198:8, 1266:25</p> <p><b>opportunity</b> <sup>[2]</sup> - 1176:17, 1228:9</p> <p><b>oppose</b> <sup>[2]</sup> - 1225:12, 1248:17</p> <p><b>opposed</b> <sup>[3]</sup> - 1056:10, 1216:14, 1226:7</p> <p><b>opposite</b> <sup>[3]</sup> - 1041:16, 1168:7, 1255:12</p> <p><b>optical</b> <sup>[1]</sup> - 1264:6</p> <p><b>optimal</b> <sup>[2]</sup> - 1021:22, 1183:21</p> <p><b>optimization</b> <sup>[1]</sup> - 1218:14</p> <p><b>optimizing</b> <sup>[2]</sup> - 1218:14</p> <p><b>options</b> <sup>[5]</sup> - 1091:3, 1091:4, 1091:11, 1091:14, 1091:15</p> <p><b>oral</b> <sup>[7]</sup> - 1111:15, 1154:16, 1196:24, 1197:6, 1256:25, 1270:1, 1271:7</p> <p><b>orally</b> <sup>[1]</sup> - 1196:15</p> <p><b>order</b> <sup>[43]</sup> - 1006:25, 1007:12, 1010:12, 1011:5, 1011:12, 1012:12, 1015:19, 1015:24, 1016:4, 1016:19, 1042:3, 1081:24, 1085:16, 1086:5, 1089:9, 1090:10, 1120:11, 1143:10, 1143:25, 1144:13, 1144:23, 1167:3, 1174:2, 1194:16, 1194:19, 1194:22, 1194:23, 1194:25, 1195:2, 1197:20, 1216:3, 1229:21, 1234:3,</p>	<p>1265:17, 1265:18, 1269:14, 1270:1, 1270:8, 1270:13, 1270:24, 1271:7</p> <p><b>ordinarily</b> <sup>[1]</sup> - 1065:9</p> <p><b>ordinary</b> <sup>[45]</sup> - 1011:20, 1012:4, 1023:13, 1024:18, 1028:17, 1029:6, 1029:8, 1032:24, 1043:10, 1045:15, 1048:12, 1049:12, 1049:24, 1050:7, 1050:14, 1051:4, 1053:6, 1062:17, 1066:16, 1069:8, 1070:2, 1072:13, 1072:15, 1100:5, 1102:9, 1103:20, 1104:7, 1104:15, 1116:13, 1116:25, 1145:3, 1145:22, 1146:4, 1146:13, 1146:19, 1147:8, 1148:19, 1149:4, 1156:2, 1156:6, 1177:16, 1180:25, 1198:10, 1227:15</p> <p><b>organism</b> <sup>[2]</sup> - 1077:6, 1077:8</p> <p><b>organisms</b> <sup>[1]</sup> - 1026:23</p> <p><b>original</b> <sup>[3]</sup> - 1027:23, 1066:23, 1073:9</p> <p><b>Ortho</b> <sup>[2]</sup> - 1233:17, 1244:10</p> <p><b>Ortho-McNeil</b> <sup>[2]</sup> - 1233:17, 1244:10</p> <p><b>Oscar</b> <sup>[1]</sup> - 1028:2</p> <p><b>otherwise</b> <sup>[2]</sup> - 1240:25, 1247:2</p> <p><b>ought</b> <sup>[4]</sup> - 1124:2, 1221:22, 1238:12, 1253:10</p> <p><b>ourselves</b> <sup>[1]</sup> - 1106:10</p> <p><b>outcome</b> <sup>[2]</sup> - 1104:17, 1184:3</p> <p><b>outcomes</b> <sup>[2]</sup> - 1091:23, 1092:5</p> <p><b>outline</b> <sup>[1]</sup> - 1028:14</p> <p><b>outlined</b> <sup>[3]</sup> - 1044:18, 1044:22, 1049:7</p> <p><b>outlining</b> <sup>[1]</sup> - 1030:6</p> <p><b>outset</b> <sup>[1]</sup> - 1052:12</p> <p><b>outside</b> <sup>[4]</sup> - 1076:23, 1166:20, 1170:15, 1182:18</p> <p><b>over-the-counter</b> <sup>[3]</sup> - 1139:9, 1139:11,</p>
---	---	---	--	---



<p>1139:17  <b>overall</b> [5] - 1133:15,  1133:24, 1134:1,  1134:7, 1143:20  <b>overemphasize</b> [1] -  1253:6  <b>overestimate</b> [1] -  1141:25  <b>overexpress</b> [5] -  1064:22, 1065:5,  1065:10, 1065:18,  1068:5  <b>overexpressing</b> [1] -  1073:21  <b>overly</b> [1] - 1078:8  <b>override</b> [1] - 1167:2  <b>oversimplified</b> [1] -  1065:8  <b>overview</b> [1] - 1031:8  <b>own</b> [4] - 1055:11,  1105:3, 1213:23,  1220:19  <b>owner</b> [1] - 1058:4  <b>oxidation</b> [1] -  1133:12  <b>oxygen</b> [1] - 1157:16</p>	<p>1115:7, 1115:11,  1115:12, 1115:17,  1115:19, 1143:14,  1144:8, 1149:17,  1153:13, 1160:20,  1161:10, 1165:20,  1263:9, 1269:15  <b>Page</b> [36] - 1007:20,  1008:5, 1008:17,  1019:25, 1035:5,  1036:1, 1037:10,  1037:15, 1038:23,  1045:6, 1047:1,  1049:17, 1050:1,  1068:22, 1073:15,  1083:4, 1083:18,  1086:8, 1086:10,  1089:25, 1094:25,  1095:13, 1115:3,  1131:7, 1152:9,  1152:13, 1156:12,  1158:24, 1160:2,  1160:9, 1160:21,  1160:24, 1161:10,  1207:25, 1208:4  <b>Pages</b> [2] - 1082:18,  1082:25  <b>pages</b> [4] - 1063:8,  1144:19, 1268:24  <b>paid</b> [1] - 1246:1  <b>Pandi</b> [8] - 1045:6,  1051:12, 1053:20,  1054:2, 1054:17,  1070:16, 1070:22,  1103:25  <b>Pandi-Perumal</b> [5] -  1045:6, 1051:12,  1053:20, 1054:2,  1054:17  <b>Pandi-Perumal</b> [3] -  1070:16, 1070:22,  1103:25  <b>PANDIPERUNAL</b> [1] -  1058:20  <b>panel</b> [6] - 1129:25,  1131:2, 1131:5,  1131:9, 1131:19,  1131:22  <b>Pani</b> [1] - 1051:6  <b>Pani-Perumal</b> [1] -  1051:6  <b>paper</b> [36] - 1071:8,  1128:5, 1128:6,  1130:2, 1130:8,  1130:9, 1136:8,  1136:18, 1136:19,  1137:3, 1137:5,  1137:14, 1140:24,  1147:17, 1147:18,  1149:12, 1149:14,</p>	<p>1150:19, 1153:13,  1159:20, 1160:1,  1164:18, 1171:14,  1171:17, 1172:11,  1173:11, 1174:8,  1174:15, 1184:8,  1184:9, 1203:22,  1204:20, 1204:24,  1205:1, 1205:2,  1218:11  <b>papers</b> [1] - 1204:23  <b>Paragraph</b> [2] -  1006:24, 1008:6  <b>paragraph</b> [11] -  1035:9, 1038:24,  1063:22, 1064:5,  1066:25, 1067:23,  1069:3, 1069:4,  1073:18, 1103:14,  1160:10  <b>paragraphs</b> [1] -  1107:6  <b>Paragraphs</b> [4] -  1006:21, 1007:7,  1007:19, 1020:1  <b>parallel</b> [1] - 1262:10  <b>parameters</b> [2] -  1217:20, 1218:3  <b>pardon</b> [1] - 1204:4  <b>parent</b> [4] - 1008:13,  1135:10, 1135:13,  1135:18  <b>parenthesis</b> [1] -  1233:3  <b>PARKINSON</b> [1] -  1126:11  <b>Parkinson</b> [32] -  1120:19, 1126:16,  1126:19, 1127:22,  1128:22, 1129:2,  1129:8, 1129:16,  1129:25, 1130:17,  1130:24, 1132:23,  1134:25, 1137:14,  1137:23, 1139:4,  1140:2, 1140:20,  1142:20, 1142:23,  1144:7, 1145:21,  1146:12, 1147:7,  1148:6, 1148:12,  1151:18, 1155:7,  1156:1, 1156:12,  1188:19, 1189:2  <b>part</b> [32] - 1013:17,  1033:22, 1049:15,  1066:10, 1071:25,  1075:7, 1092:22,  1095:3, 1100:22,  1108:19, 1108:21,  1116:21, 1117:6,</p>	<p>1126:11, 1132:12,  1132:25, 1133:24,  1143:4, 1151:18,  1169:22, 1171:19,  1172:14, 1182:3,  1205:3, 1218:13,  1228:21, 1229:16,  1235:25, 1247:4,  1262:21, 1266:22  <b>partial</b> [2] - 1221:22,  1221:23  <b>partially</b> [1] - 1032:5  <b>participants</b> [1] -  1170:13  <b>participate</b> [1] -  1118:18  <b>participated</b> [1] -  1207:15  <b>particular</b> [30] -  1012:23, 1017:20,  1028:16, 1029:17,  1031:2, 1032:25,  1035:9, 1049:23,  1051:15, 1055:21,  1063:11, 1081:8,  1081:13, 1136:20,  1141:13, 1146:10,  1154:15, 1170:11,  1173:10, 1174:14,  1184:25, 1185:6,  1228:23, 1232:7,  1232:9, 1253:6,  1254:20, 1255:17,  1258:9  <b>particularly</b> [5] -  1067:20, 1067:21,  1164:9, 1241:10,  1244:19  <b>parties</b> [5] - 1058:4,  1121:19, 1228:21,  1270:14, 1271:11  <b>parties</b> [1] - 1162:25  <b>partners</b> [1] - 1267:22  <b>parts</b> [1] - 1094:17  <b>party</b> [1] - 1017:23  <b>pass</b> [6] - 1014:1,  1030:7, 1030:14,  1052:3, 1214:11,  1220:15  <b>passage</b> [1] - 1083:16  <b>passages</b> [1] -  1050:23  <b>passed</b> [4] - 1133:3,  1229:22, 1232:16,  1242:18  <b>past</b> [3] - 1056:13,  1076:25, 1164:5  <b>patent</b> [121] - 1006:19,  1007:4, 1008:2,  1008:4, 1008:5,</p>	<p>1008:9, 1008:15,  1009:1, 1009:12,  1010:10, 1010:11,  1010:12, 1010:14,  1010:19, 1010:25,  1011:9, 1011:10,  1013:2, 1013:6,  1015:9, 1015:10,  1015:14, 1015:17,  1015:19, 1015:22,  1015:23, 1016:9,  1017:9, 1017:20,  1018:17, 1020:15,  1020:18, 1021:10,  1021:16, 1029:2,  1049:4, 1050:12,  1050:21, 1053:1,  1053:18, 1053:19,  1055:6, 1059:10,  1060:1, 1060:12,  1060:23, 1062:19,  1063:3, 1100:3,  1100:6, 1102:10,  1102:16, 1106:16,  1129:11, 1129:14,  1140:3, 1140:7,  1155:8, 1155:11,  1155:20, 1180:11,  1184:8, 1184:13,  1184:16, 1188:5,  1188:22, 1189:8,  1189:13, 1189:15,  1189:19, 1190:10,  1190:12, 1190:13,  1191:4, 1191:10,  1191:12, 1195:19,  1223:23, 1223:25,  1224:15, 1226:21,  1227:1, 1227:7,  1227:10, 1228:13,  1228:25, 1229:22,  1232:5, 1232:12,  1232:16, 1232:22,  1233:23, 1234:9,  1235:4, 1236:22,  1240:13, 1240:23,  1241:7, 1241:16,  1241:24, 1245:17,  1245:18, 1246:20,  1247:21, 1248:20,  1254:5, 1256:11,  1256:13, 1256:20,  1258:13, 1258:18,  1259:1, 1259:7,  1259:8, 1261:3,  1263:20, 1263:25,  1265:1, 1271:17  <b>patentable</b> [3] -  1258:16, 1259:10,  1259:12  <b>patentee</b> [1] - 1256:17</p>
<b>P</b>				
<p><b>P-I-C-O-M-O-L-A-R</b> [1]  - 1035:22  <b>p.m</b> [10] - 1167:14,  1167:19, 1167:23,  1173:7, 1173:13,  1173:15, 1179:11,  1182:10, 1182:11,  1272:3  <b>P450</b> [21] - 1031:5,  1031:10, 1060:25,  1073:9, 1114:19,  1131:3, 1131:16,  1132:14, 1132:16,  1133:20, 1133:23,  1136:20, 1136:22,  1141:17, 1142:6,  1143:18, 1143:19,  1145:24, 1147:21,  1153:22, 1160:12  <b>pacemaker</b> [4] -  1163:25, 1164:14,  1202:25, 1217:16  <b>package</b> [3] - 1100:13,  1262:24, 1263:4  <b>page</b> [29] - 1006:16,  1007:20, 1008:16,  1061:17, 1082:19,  1082:20, 1082:22,  1082:23, 1094:12,  1096:8, 1107:10,  1114:11, 1114:14,</p>				

<p><b>patents</b> [16] - 1028:16, 1028:22, 1029:7, 1057:2, 1059:3, 1068:2, 1072:22, 1088:16, 1092:3, 1155:8, 1155:20, 1188:15, 1191:17, 1224:14, 1259:2, 1268:1</p> <p><b>pathway</b> [1] - 1077:21</p> <p><b>pathways</b> [5] - 1132:17, 1133:1, 1134:1, 1134:4, 1134:10</p> <p><b>patient</b> [22] - 1049:7, 1050:24, 1059:23, 1085:21, 1091:24, 1178:22, 1186:11, 1192:1, 1192:3, 1192:8, 1192:17, 1194:17, 1195:3, 1196:7, 1196:8, 1196:9, 1196:15, 1196:24, 1197:4, 1197:9, 1198:3, 1212:16</p> <p><b>patients</b> [22] - 1153:24, 1167:21, 1168:6, 1191:8, 1194:4, 1200:1, 1201:23, 1208:13, 1208:18, 1209:22, 1209:24, 1212:1, 1212:9, 1212:14, 1218:1, 1218:8, 1218:24, 1219:6, 1220:20, 1222:13, 1258:14, 1262:7</p> <p><b>pattern</b> [5] - 1222:2, 1222:4, 1222:5, 1222:14, 1222:15</p> <p><b>PAUL</b> [1] - 1005:8</p> <p><b>pause</b> [3] - 1064:23, 1176:14, 1188:10</p> <p><b>pay</b> [1] - 1031:4</p> <p><b>pays</b> [1] - 1213:6</p> <p><b>PDX</b> [2] - 1137:21, 1141:3</p> <p><b>PDX-10.10</b> [1] - 1130:22</p> <p><b>PDX-10.12</b> [1] - 1132:21</p> <p><b>PDX-10.14</b> [1] - 1134:23</p> <p><b>PDX-10.18</b> [1] - 1140:5</p> <p><b>PDX-10.19</b> [1] - 1140:18</p> <p><b>PDX-11.13</b> [1] - 1170:5</p> <p><b>PDX-11.14</b> [1] - 1199:10</p>	<p><b>PDX-11.17</b> [1] - 1199:14</p> <p><b>PDX-11.21</b> [1] - 1200:12</p> <p><b>PDX-11.25</b> [1] - 1201:5</p> <p><b>PDX-17</b> [1] - 1200:3</p> <p><b>peak</b> [1] - 1172:15</p> <p><b>peaking</b> [1] - 1203:2</p> <p><b>peaks</b> [1] - 1185:2</p> <p><b>peer</b> [2] - 1062:10, 1062:14</p> <p><b>peer-reviewed</b> [2] - 1062:10, 1062:14</p> <p><b>pellet</b> [3] - 1034:5, 1065:23</p> <p><b>people</b> [54] - 1007:24, 1008:21, 1014:18, 1015:3, 1015:18, 1077:16, 1090:15, 1094:20, 1095:18, 1098:18, 1113:22, 1164:25, 1165:2, 1167:10, 1167:12, 1168:14, 1171:4, 1171:9, 1173:6, 1173:19, 1179:18, 1180:7, 1180:25, 1182:8, 1183:7, 1185:24, 1186:15, 1186:21, 1186:24, 1187:14, 1187:19, 1187:20, 1199:23, 1200:22, 1202:2, 1202:3, 1202:6, 1203:16, 1210:5, 1210:15, 1212:3, 1214:17, 1214:20, 1214:22, 1222:22, 1223:5, 1224:10, 1225:9, 1245:19, 1253:21, 1259:12, 1262:15, 1263:3</p> <p><b>per</b> [1] - 1268:24</p> <p><b>percent</b> [47] - 1010:5, 1010:18, 1010:23, 1015:15, 1015:16, 1017:10, 1021:16, 1022:1, 1022:22, 1023:4, 1023:10, 1023:14, 1023:24, 1024:2, 1024:3, 1024:19, 1024:23, 1032:4, 1046:15, 1076:11, 1076:12, 1097:14, 1097:24, 1111:5, 1111:7, 1133:15, 1133:23, 1134:1, 1134:15, 1138:5, 1138:6, 1138:7, 1143:19,</p>	<p>1146:5, 1146:16, 1146:22, 1147:2, 1147:4, 1148:1, 1148:15, 1194:6, 1194:8, 1218:7, 1218:12, 1219:5</p> <p><b>percentage</b> [6] - 1055:22, 1146:8, 1146:9, 1146:24, 1147:5, 1147:11</p> <p><b>perfect</b> [1] - 1095:11</p> <p><b>perfectly</b> [1] - 1062:24</p> <p><b>perform</b> [1] - 1232:2</p> <p><b>performing</b> [1] - 1232:23</p> <p><b>perhaps</b> [7] - 1014:16, 1087:18, 1091:13, 1148:17, 1196:4, 1200:13, 1229:7</p> <p><b>Peribonal</b> [1] - 1038:9</p> <p><b>period</b> [32] - 1118:6, 1164:22, 1165:4, 1165:22, 1166:17, 1166:18, 1166:24, 1167:7, 1167:10, 1167:13, 1167:22, 1168:1, 1168:4, 1168:9, 1168:12, 1168:15, 1175:11, 1179:22, 1183:7, 1196:10, 1200:23, 1201:6, 1201:10, 1227:1, 1227:10, 1227:16, 1228:2, 1228:5, 1228:9, 1239:24</p> <p><b>permanently</b> [1] - 1183:24</p> <p><b>Perni</b> [1] - 1239:16</p> <p><b>Perni's</b> [1] - 1261:9</p> <p><b>perpetrator</b> [2] - 1041:7, 1152:5</p> <p><b>perpetrators</b> [3] - 1151:13, 1151:23, 1152:3</p> <p><b>person</b> [63] - 1010:21, 1011:20, 1012:4, 1012:11, 1012:12, 1012:17, 1013:7, 1029:8, 1032:23, 1043:10, 1045:15, 1048:12, 1049:12, 1049:23, 1050:7, 1050:14, 1051:4, 1053:6, 1054:14, 1054:16, 1054:20, 1056:24, 1059:15, 1059:22, 1061:23, 1062:17, 1064:8, 1066:16, 1066:21,</p>	<p>1069:7, 1070:1, 1072:13, 1072:15, 1100:5, 1102:7, 1102:15, 1103:20, 1104:7, 1104:16, 1113:6, 1116:13, 1116:25, 1145:2, 1145:22, 1146:4, 1146:13, 1146:19, 1147:8, 1148:19, 1149:4, 1156:2, 1156:6, 1164:18, 1177:7, 1177:16, 1183:23, 1191:5, 1194:24, 1195:9, 1198:9, 1228:3, 1228:6, 1236:16</p> <p><b>personally</b> [2] - 1013:11, 1216:10</p> <p><b>pertinent</b> [3] - 1012:18, 1012:21, 1072:19</p> <p><b>Perumal</b> [6] - 1045:6, 1051:6, 1051:12, 1053:20, 1054:2, 1054:17</p> <p><b>Perunal</b> [3] - 1070:16, 1070:22, 1103:25</p> <p><b>pervasive</b> [1] - 1201:18</p> <p><b>Pfizer</b> [2] - 1040:2, 1058:4</p> <p><b>pharmaceutical</b> [15] - 1010:15, 1010:25, 1011:22, 1013:2, 1013:6, 1013:9, 1113:23, 1113:25, 1127:5, 1127:8, 1128:15, 1128:19, 1145:12, 1262:5, 1262:15</p> <p><b>pharmaceutical-grade</b> [3] - 1013:2, 1013:6, 1013:9</p> <p><b>pharmaceuticals</b> [1] - 1259:16</p> <p><b>PHARMACEUTICAL S</b> [2] - 1:5, 1:7</p> <p><b>Pharmaceuticals</b> [3] - 1005:6, 1005:13, 1160:6</p> <p><b>pharmacokinetic</b> [3] - 1106:6, 1135:11, 1135:17</p> <p><b>Pharmacokinetics</b> [2] - 1064:6, 1072:4</p> <p><b>pharmacokinetics</b> [5] - 1028:19, 1029:11, 1106:3, 1128:23, 1150:24</p> <p><b>pharmacologic</b> [5] -</p>	<p>1035:12, 1078:24, 1079:4, 1079:10, 1135:10</p> <p><b>pharmacologically</b> [1] - 1135:20</p> <p><b>pharmacologist</b> [1] - 1029:13</p> <p><b>pharmacology</b> [14] - 1026:19, 1026:21, 1026:22, 1026:25, 1027:3, 1028:3, 1028:7, 1029:11, 1035:8, 1037:9, 1037:11, 1040:7, 1127:23, 1128:23</p> <p><b>Pharmacology</b> [2] - 1027:12, 1027:19</p> <p><b>phase</b> [49] - 1150:12, 1166:5, 1167:21, 1168:6, 1168:17, 1168:18, 1168:22, 1170:9, 1170:12, 1170:18, 1171:2, 1171:8, 1171:11, 1172:10, 1172:13, 1172:15, 1172:16, 1173:5, 1173:10, 1173:18, 1173:21, 1173:22, 1175:9, 1175:16, 1175:22, 1177:4, 1177:15, 1178:5, 1180:22, 1181:4, 1182:4, 1183:5, 1183:6, 1183:16, 1183:24, 1190:4, 1199:15, 1200:18, 1201:6, 1201:11, 1202:9, 1203:16, 1204:8, 1220:10</p> <p><b>Phase</b> [1] - 1096:12</p> <p><b>phases</b> [4] - 1093:24, 1096:5, 1096:7, 1184:1</p> <p><b>PhD</b> [1] - 1163:17</p> <p><b>phenomenon</b> [1] - 1138:14</p> <p><b>phrase</b> [4] - 1240:21, 1242:16, 1242:25, 1247:4</p> <p><b>phrases</b> [1] - 1049:7</p> <p><b>physician</b> [3] - 1025:21, 1212:11, 1219:15</p> <p><b>physicians</b> [4] - 1042:4, 1210:12, 1217:23, 1221:3</p> <p><b>pick</b> [7] - 1054:20, 1118:10, 1181:20, 1220:18, 1251:6,</p>
---	---	--	--	---

<p>1268:17, 1270:15  <b>PICKARD</b> [1] - 1005:4  <b>picomolar</b> [2] -  1035:16, 1035:20  <b>picture</b> [7] - 1082:6,  1082:9, 1082:13,  1083:25, 1084:4,  1084:5, 1134:7  <b>pictures</b> [1] - 1265:10  <b>piece</b> [4] - 1012:23,  1034:2, 1078:9,  1083:24  <b>pieces</b> [1] - 1263:6  <b>pill</b> [1] - 1177:19  <b>pin</b> [2] - 1067:22,  1068:17  <b>pioneering</b> [1] -  1208:11  <b>place</b> [11] - 1030:23,  1055:2, 1064:10,  1069:1, 1144:24,  1203:9, 1235:21,  1240:23, 1242:5,  1242:7, 1260:24  <b>placebo</b> [2] - 1171:1,  1175:18  <b>places</b> [3] - 1232:18,  1238:4, 1242:13  <b>plain</b> [5] - 1227:15,  1249:20, 1251:17,  1255:4, 1255:7  <b>Plaintiff</b> [2] - 1:5,  1126:12  <b>plaintiff</b> [9] - 1015:7,  1016:2, 1124:10,  1125:3, 1185:19,  1205:21, 1224:1,  1255:24, 1265:17  <b>Plaintiffs</b> [1] -  1169:10  <b>plaintiffs</b> [3] -  1079:18, 1080:10,  1171:22  <b>plaintiffs</b> [3] - 1016:1,  1205:15, 1255:5  <b>plan</b> [4] - 1028:14,  1079:14, 1129:8,  1130:18  <b>plane</b> [1] - 1177:23  <b>planned</b> [1] - 1130:18  <b>plasma</b> [5] - 1044:14,  1044:16, 1045:9,  1046:13, 1104:12  <b>plateau</b> [1] - 1142:7  <b>play</b> [1] - 1230:23  <b>pleading</b> [1] - 1017:22  <b>pleadings</b> [2] -  1016:3, 1017:24  <b>pleasure</b> [1] - 1190:21  <b>plenty</b> [2] - 1059:20,</p>	<p>1252:24  <b>pleural</b> [1] - 1057:18  <b>plus</b> [3] - 1092:23,  1134:15, 1230:14  <b>point</b> [56] - 1010:1,  1016:12, 1017:1,  1017:18, 1021:20,  1049:21, 1054:24,  1059:21, 1059:24,  1060:8, 1063:10,  1072:20, 1097:21,  1098:8, 1125:22,  1130:15, 1144:20,  1152:7, 1158:7,  1158:17, 1172:17,  1173:10, 1174:14,  1174:20, 1180:6,  1191:19, 1192:13,  1195:14, 1200:15,  1200:22, 1201:15,  1202:10, 1215:15,  1217:18, 1221:1,  1230:17, 1235:2,  1240:21, 1241:13,  1241:23, 1243:11,  1243:12, 1243:13,  1248:22, 1251:19,  1253:14, 1254:13,  1254:22, 1258:25,  1260:18, 1261:7,  1264:7, 1269:17,  1270:3, 1270:25  <b>pointed</b> [3] - 1214:16,  1230:1, 1232:18  <b>points</b> [2] - 1090:22,  1188:13  <b>policy</b> [3] - 1163:20,  1245:16, 1248:25  <b>polymeropoulos</b> [2] -  1114:5, 1181:22  <b>polypropylene</b> [1] -  1006:24  <b>portal</b> [1] - 1030:21  <b>portion</b> [12] - 1130:3,  1177:14, 1178:5,  1180:22, 1183:4,  1183:16, 1201:5,  1204:8, 1237:17,  1244:20, 1268:9  <b>portions</b> [1] - 1270:3  <b>POSA</b> [4] - 1010:17,  1057:7, 1145:18,  1254:17  <b>POSAs</b> [1] - 1057:3  <b>POSITA</b> [3] - 1238:15,  1238:17  <b>position</b> [5] - 1143:8,  1143:23, 1144:21,  1243:4, 1243:25  <b>positions</b> [1] - 1027:6</p>	<p><b>positive</b> [1] - 1141:18  <b>possessive</b> [1] -  1057:18  <b>possibility</b> [3] -  1048:18, 1101:20,  1102:4  <b>possible</b> [23] - 1023:3,  1042:5, 1043:6,  1043:15, 1050:18,  1068:9, 1068:24,  1072:18, 1076:15,  1077:17, 1077:19,  1079:7, 1080:22,  1133:25, 1134:18,  1135:21, 1150:4,  1177:13, 1193:23,  1195:6, 1195:25,  1213:20, 1244:18  <b>possibly</b> [3] - 1055:9,  1061:13, 1104:12  <b>postdoctoral</b> [1] -  1163:19  <b>posture</b> [1] - 1225:17  <b>pot</b> [3] - 1231:19,  1231:22, 1233:8  <b>potential</b> [3] -  1028:25, 1135:1,  1159:9  <b>potentially</b> [1] -  1124:6  <b>powerful</b> [1] - 1170:18  <b>practical</b> [2] - 1079:2,  1254:7  <b>practice</b> [15] - 1032:5,  1037:8, 1042:1,  1059:19, 1086:25,  1094:1, 1145:17,  1153:16, 1194:22,  1196:23, 1197:14,  1197:15, 1217:20,  1218:3, 1221:7  <b>practiced</b> [1] -  1197:12  <b>practicing</b> [4] -  1027:2, 1194:23,  1195:4, 1196:1  <b>PRC</b> [4] - 1170:22,  1181:17, 1181:18,  1181:25  <b>PRCs</b> [1] - 1170:19  <b>preamble</b> [1] -  1195:21  <b>precedent</b> [1] -  1252:17  <b>precedes</b> [1] - 1118:1  <b>precise</b> [1] - 1261:9  <b>precisely</b> [5] -  1085:25, 1158:5,  1231:5, 1260:5,  1263:2</p>	<p><b>Preclinical</b> [1] -  1072:3  <b>preclinical</b> [1] -  1093:23  <b>preclude</b> [2] -  1118:15, 1120:25  <b>precludes</b> [1] - 1252:1  <b>predict</b> [8] - 1051:23,  1098:15, 1098:16,  1098:20, 1119:12,  1152:20, 1153:4,  1153:9  <b>predicted</b> [1] -  1150:11  <b>prediction</b> [2] -  1099:23, 1150:3  <b>Prediction</b> [1] -  1149:25  <b>prefer</b> [1] - 1216:23  <b>preferred</b> [2] -  1245:13, 1253:4  <b>prejudice</b> [1] -  1271:16  <b>prejudiced</b> [2] -  1018:12, 1125:17  <b>prejudicial</b> [1] -  1016:22  <b>premise</b> [1] - 1012:3  <b>premises</b> [1] -  1011:19  <b>prepare</b> [9] - 1007:8,  1007:21, 1025:14,  1030:6, 1031:7,  1040:6, 1132:18,  1136:2, 1231:24  <b>prepared</b> [4] - 1008:8,  1129:3, 1130:24,  1166:6  <b>preparing</b> [1] -  1166:25  <b>prescribe</b> [2] - 1143:1,  1212:14  <b>prescribed</b> [3] -  1142:23, 1214:20,  1220:1  <b>prescription</b> [2] -  1139:10, 1215:3  <b>presence</b> [1] - 1252:2  <b>present</b> [4] - 1032:2,  1085:18, 1181:9,  1207:7  <b>presentation</b> [3] -  1147:18, 1148:8,  1225:8  <b>presenting</b> [1] -  1162:25  <b>presents</b> [1] - 1178:22  <b>preserve</b> [2] -  1247:20, 1248:6  <b>preserving</b> [1] -</p>	<p>1225:19  <b>president</b> [1] -  1027:18  <b>presumably</b> [1] -  1222:6  <b>presume</b> [1] - 1122:6  <b>presumed</b> [1] -  1012:17  <b>pretend</b> [1] - 1254:12  <b>pretrial</b> [4] - 1015:24,  1016:3, 1016:19,  1216:3  <b>pretty</b> [6] - 1021:21,  1022:17, 1075:21,  1234:14, 1239:19,  1239:20  <b>prevalent</b> [1] - 1054:3  <b>previous</b> [4] -  1126:24, 1138:11,  1144:18, 1170:12  <b>previously</b> [7] -  1018:25, 1039:13,  1172:13, 1186:7,  1192:23, 1215:21,  1257:14  <b>primarily</b> [10] -  1036:8, 1061:4,  1066:7, 1066:19,  1067:24, 1073:25,  1074:20, 1074:23,  1114:21, 1115:22  <b>primary</b> [22] - 1016:16,  1049:11, 1051:3,  1052:23, 1052:25,  1053:19, 1054:11,  1055:12, 1055:19,  1055:22, 1055:25,  1056:14, 1056:24,  1062:18, 1063:18,  1063:21, 1072:18,  1074:11, 1075:2,  1075:4, 1130:10,  1164:13  <b>principal</b> [3] - 1039:3,  1040:23, 1049:19  <b>principally</b> [1] -  1256:10  <b>principle</b> [1] - 1244:24  <b>principles</b> [2] -  1256:4, 1256:8  <b>prioritize</b> [1] - 1268:17  <b>priority</b> [20] - 1017:12,  1042:11, 1050:17,  1053:7, 1059:3,  1059:9, 1073:7,  1092:3, 1092:8,  1092:17, 1093:17,  1097:1, 1097:21,  1098:2, 1098:10,  1100:5, 1101:7,</p>
---	--	---	---	---

<p>1106:16, 1199:3, 1256:14</p> <p><b>probable</b> [1] - 1104:10</p> <p><b>problem</b> [18] - 1024:5, 1052:6, 1053:10, 1088:24, 1118:25, 1124:23, 1141:24, 1202:18, 1231:14, 1240:3, 1240:4, 1249:17, 1249:23, 1251:7, 1263:22, 1266:22, 1266:24</p> <p><b>procedural</b> [1] - 1225:17</p> <p><b>procedure</b> [3] - 1020:24, 1021:5, 1022:18</p> <p><b>proceed</b> [9] - 1019:16, 1023:20, 1050:6, 1080:6, 1118:9, 1118:23, 1119:19, 1142:17, 1259:22</p> <p><b>proceeding</b> [3] - 1130:18, 1272:2, 1272:6</p> <p><b>proceedings</b> [1] - 1102:13</p> <p><b>process</b> [52] - 1006:18, 1007:15, 1008:7, 1009:4, 1009:6, 1009:9, 1009:17, 1009:18, 1009:21, 1010:2, 1010:3, 1010:24, 1011:5, 1011:8, 1016:9, 1020:10, 1020:19, 1021:9, 1021:14, 1033:1, 1033:21, 1105:21, 1128:19, 1218:14, 1220:23, 1228:22, 1229:2, 1229:5, 1230:22, 1231:21, 1231:23, 1232:1, 1232:3, 1233:2, 1233:5, 1234:2, 1235:17, 1259:22, 1259:25, 1260:11, 1260:17, 1260:18, 1260:20, 1261:15, 1261:25, 1262:6, 1262:11, 1262:12, 1262:18, 1262:19, 1263:10, 1263:22</p> <p><b>processes</b> [3] - 1201:25, 1245:14, 1260:4</p> <p><b>processing</b> [3] - 1164:23, 1167:7, 1168:15</p>	<p><b>prodrugs</b> [1] - 1079:13</p> <p><b>produce</b> [7] - 1016:10, 1016:13, 1016:14, 1021:11, 1035:11, 1066:4, 1078:21</p> <p><b>produced</b> [1] - 1023:3</p> <p><b>produces</b> [1] - 1251:10</p> <p><b>producing</b> [1] - 1041:15</p> <p><b>product</b> [25] - 1008:23, 1011:12, 1012:25, 1013:12, 1013:18, 1015:20, 1036:21, 1042:7, 1117:8, 1211:7, 1228:22, 1229:5, 1230:22, 1231:21, 1231:23, 1232:1, 1232:3, 1233:2, 1233:5, 1233:10, 1234:2, 1251:2, 1251:12, 1251:15, 1263:19</p> <p><b>product-by-process</b> [10] - 1228:22, 1229:5, 1230:22, 1231:21, 1231:23, 1232:1, 1232:3, 1233:2, 1233:5, 1234:2</p> <p><b>products</b> [2] - 1011:22, 1013:9</p> <p><b>professionally</b> [1] - 1105:14</p> <p><b>Professor</b> [1] - 1163:10</p> <p><b>professor</b> [5] - 1025:22, 1126:20, 1127:23, 1128:2, 1128:3</p> <p><b>proffered</b> [2] - 1264:8, 1264:21</p> <p><b>profile</b> [1] - 1021:12</p> <p><b>Profile</b> [1] - 1062:4</p> <p><b>profiles</b> [1] - 1115:20</p> <p><b>programmed</b> [1] - 1065:16</p> <p><b>programming</b> [1] - 1065:8</p> <p><b>progresses</b> [1] - 1203:2</p> <p><b>prominent</b> [1] - 1136:23</p> <p><b>prominently</b> [1] - 1161:15</p> <p><b>promise</b> [2] - 1058:8, 1215:19</p> <p><b>promoting</b> [1] -</p>	<p>1187:22</p> <p><b>promptly</b> [1] - 1018:21</p> <p><b>pronounce</b> [1] - 1062:1</p> <p><b>pronunciation</b> [1] - 1058:23</p> <p><b>propensity</b> [1] - 1202:20</p> <p><b>proper</b> [5] - 1119:19, 1177:6, 1240:20, 1244:5, 1244:6</p> <p><b>properties</b> [1] - 1078:22</p> <p><b>propionic</b> [1] - 1021:6</p> <p><b>propionylating</b> [1] - 1007:4</p> <p><b>proportion</b> [1] - 1218:1</p> <p><b>proposed</b> [4] - 1249:18, 1252:5, 1269:14, 1271:3</p> <p><b>proposition</b> [1] - 1252:22</p> <p><b>prosecution</b> [1] - 1015:9</p> <p><b>protocol</b> [3] - 1182:14, 1182:21, 1182:23</p> <p><b>prototype</b> [1] - 1043:8</p> <p><b>provide</b> [10] - 1086:5, 1089:9, 1090:10, 1090:17, 1091:24, 1134:8, 1138:16, 1139:4, 1212:22, 1269:18</p> <p><b>provided</b> [3] - 1056:23, 1069:9, 1216:15</p> <p><b>provides</b> [2] - 1017:23, 1247:18</p> <p><b>providing</b> [2] - 1036:13, 1141:12</p> <p><b>psychiatric</b> [2] - 1154:21, 1187:19</p> <p><b>psychiatry</b> [1] - 1029:23</p> <p><b>Psychopharmacology</b> [1] - 1027:15</p> <p><b>PTX-10.3</b> [1] - 1129:6</p> <p><b>PTX-10.9</b> [1] - 1129:23</p> <p><b>PTX-263</b> [4] - 1207:24, 1209:6, 1209:14, 1209:17</p> <p><b>PTX-393</b> [7] - 1136:25, 1137:8, 1137:12, 1139:20, 1139:21, 1139:24, 1154:11</p> <p><b>PTX-394</b> [5] - 1136:3, 1136:10, 1136:14, 1139:21, 1139:25</p> <p><b>PTX-513</b> [3] - 1185:16,</p>	<p>1185:20, 1185:23</p> <p><b>PTX-613</b> [1] - 1114:2</p> <p><b>PTX-683</b> [3] - 1099:4, 1099:13, 1099:16</p> <p><b>PTX-824</b> [2] - 1169:5, 1169:13</p> <p><b>PTX-827</b> [2] - 1127:12, 1127:17</p> <p><b>pTX-827</b> [1] - 1127:20</p> <p><b>PTX-829</b> [1] - 1014:7</p> <p><b>pTX-829</b> [1] - 1014:11</p> <p><b>PTX-830</b> [1] - 1014:11</p> <p><b>public</b> [7] - 1092:6, 1097:22, 1118:25, 1119:18, 1119:20, 1156:5, 1156:10</p> <p><b>publically</b> [2] - 1055:1, 1073:12</p> <p><b>publication</b> [8] - 1036:15, 1036:16, 1039:20, 1106:8, 1106:9, 1136:6, 1152:9, 1153:14</p> <p><b>publications</b> [2] - 1027:21, 1027:23</p> <p><b>publish</b> [1] - 1113:23</p> <p><b>published</b> [9] - 1027:20, 1061:19, 1098:23, 1106:12, 1164:18, 1169:20, 1171:14, 1204:21, 1204:23</p> <p><b>pull</b> [19] - 1006:15, 1020:1, 1071:25, 1073:18, 1107:9, 1129:6, 1129:22, 1132:20, 1137:20, 1140:4, 1140:17, 1141:2, 1150:15, 1156:12, 1159:16, 1191:20, 1199:7, 1204:25, 1249:11</p> <p><b>pulling</b> [1] - 1199:9</p> <p><b>pulse</b> [1] - 1189:21</p> <p><b>pure</b> [7] - 1011:6, 1011:12, 1015:15, 1022:1, 1024:8, 1230:13, 1263:19</p> <p><b>purely</b> [1] - 1059:17</p> <p><b>purification</b> [1] - 1022:18</p> <p><b>purified</b> [1] - 1013:2</p> <p><b>purify</b> [1] - 1012:24</p> <p><b>purity</b> [9] - 1017:10, 1021:15, 1021:22, 1022:2, 1022:4, 1022:5, 1022:8, 1022:22, 1024:19</p> <p><b>purple</b> [1] - 1044:18</p> <p><b>purpose</b> [1] - 1102:12</p>	<p><b>purposes</b> [5] - 1079:2, 1086:25, 1219:9, 1226:10, 1270:24</p> <p><b>pursuant</b> [1] - 1162:24</p> <p><b>put</b> [41] - 1015:7, 1016:8, 1016:18, 1019:2, 1033:12, 1053:22, 1057:24, 1061:16, 1065:3, 1067:22, 1068:17, 1080:14, 1085:13, 1088:20, 1099:8, 1104:21, 1109:18, 1115:6, 1125:20, 1147:15, 1149:9, 1170:24, 1179:2, 1225:4, 1231:21, 1231:22, 1237:17, 1238:6, 1241:5, 1243:1, 1243:23, 1244:1, 1245:8, 1249:18, 1251:12, 1254:20, 1262:24, 1263:8, 1264:16, 1265:15, 1270:8</p> <p><b>puts</b> [1] - 1264:16</p> <p><b>putting</b> [4] - 1231:11, 1231:18, 1233:3, 1233:8</p> <p><b>puzzle</b> [1] - 1132:12</p> <p><b>puzzled</b> [1] - 1194:13</p>
				<b>Q</b>
				<p><b>qualification</b> [1] - 1102:18</p> <p><b>quantitative</b> [5] - 1032:6, 1052:1, 1085:25, 1098:16, 1098:20</p> <p><b>quantitatively</b> [2] - 1152:20, 1153:4</p> <p><b>questions</b> [22] - 1014:3, 1019:11, 1023:7, 1033:4, 1068:11, 1068:14, 1116:2, 1116:9, 1117:14, 1117:17, 1128:5, 1142:14, 1158:7, 1158:8, 1161:24, 1190:15, 1214:10, 1214:25, 1216:22, 1221:13, 1249:6, 1257:25</p> <p><b>quickly</b> [5] - 1080:24, 1114:11, 1154:11, 1263:13, 1272:1</p> <p><b>quite</b> [6] - 1021:21, 1076:8, 1164:24, 1190:23, 1242:19,</p>



1246:8 <b>quote</b> [8] - 1032:8, 1045:3, 1046:25, 1049:16, 1050:1, 1071:4, 1074:10, 1093:25	1157:15, 1157:22, 1211:13, 1211:20, 1211:25 <b>ramelteon's</b> [1] - 1104:18 <b>range</b> [4] - 1031:20, 1037:17, 1037:18, 1111:7 <b>rapidly</b> [1] - 1178:1 <b>rat</b> [4] - 1077:9, 1077:11, 1077:14, 1202:22 <b>ratchet</b> [1] - 1125:12 <b>rate</b> [1] - 1037:16 <b>rather</b> [7] - 1015:25, 1071:11, 1084:11, 1084:14, 1200:17, 1201:18, 1202:11 <b>raw</b> [1] - 1106:10 <b>RE604</b> [3] - 1189:24, 1190:12, 1195:18 <b>reach</b> [5] - 1142:7, 1183:21, 1244:23, 1248:8, 1257:11 <b>reached</b> [1] - 1217:21 <b>reaches</b> [2] - 1111:15, 1150:12 <b>react</b> [19] - 1007:11, 1176:4, 1229:21, 1230:12, 1230:19, 1236:17, 1236:18, 1241:6, 1243:2, 1249:24, 1250:12, 1250:13, 1252:6, 1252:8, 1252:9, 1255:8 <b>reacted</b> [3] - 1230:14, 1250:21, 1270:19 <b>reacting</b> [45] - 1227:6, 1229:20, 1230:3, 1230:4, 1230:18, 1231:1, 1231:7, 1231:9, 1231:12, 1231:18, 1232:10, 1232:11, 1232:18, 1232:19, 1233:12, 1233:13, 1233:16, 1233:23, 1239:9, 1239:21, 1240:9, 1240:22, 1240:24, 1241:8, 1241:16, 1242:2, 1242:10, 1242:16, 1242:17, 1242:24, 1243:1, 1243:7, 1243:16, 1243:17, 1250:1, 1251:1, 1251:2, 1251:9, 1252:7, 1252:13, 1252:14, 1252:19, 1255:20,	1255:22, 1256:23 <b>reaction</b> [23] - 1007:22, 1008:18, 1014:23, 1035:19, 1078:16, 1230:9, 1230:12, 1233:19, 1235:4, 1235:7, 1237:16, 1240:25, 1242:8, 1242:9, 1251:2, 1251:10, 1252:1, 1252:4, 1253:2, 1253:19, 1255:13, 1255:25, 1265:4 <b>reactions</b> [6] - 1015:1, 1026:24, 1047:21, 1232:8, 1233:8, 1235:16 <b>read</b> [29] - 1054:14, 1070:12, 1072:16, 1082:25, 1086:9, 1144:18, 1161:1, 1186:20, 1193:16, 1236:21, 1236:22, 1239:22, 1240:12, 1243:6, 1243:8, 1245:7, 1246:6, 1246:22, 1247:14, 1247:21, 1248:8, 1248:16, 1253:15, 1254:5, 1254:8, 1255:5, 1256:4, 1266:4 <b>reader</b> [2] - 1067:23, 1229:6 <b>reading</b> [17] - 1007:24, 1064:8, 1066:16, 1074:11, 1092:17, 1102:7, 1103:6, 1103:21, 1130:8, 1182:23, 1230:7, 1233:6, 1245:12, 1248:20, 1252:18, 1255:3, 1270:18 <b>reads</b> [1] - 1256:9 <b>ready</b> [4] - 1083:2, 1083:3, 1228:18, 1235:5 <b>reagents</b> [2] - 1253:6, 1254:20 <b>real</b> [3] - 1139:5, 1177:6, 1231:14 <b>real-world</b> [1] - 1139:5 <b>realize</b> [1] - 1248:19 <b>really</b> [29] - 1022:1, 1022:3, 1022:9, 1022:23, 1034:7, 1075:17, 1113:8, 1124:17, 1153:1, 1171:2, 1174:21,	1177:13, 1182:12, 1214:15, 1217:18, 1224:4, 1226:22, 1240:5, 1243:5, 1244:18, 1245:15, 1245:23, 1251:17, 1253:12, 1255:3, 1256:7, 1266:16, 1266:17 <b>reason</b> [16] - 1018:16, 1049:20, 1060:9, 1061:12, 1141:5, 1154:20, 1175:19, 1175:23, 1184:4, 1203:15, 1211:1, 1216:17, 1225:16, 1230:10, 1240:25, 1259:14 <b>reasonable</b> [11] - 1061:6, 1113:12, 1143:5, 1143:10, 1143:25, 1144:13, 1144:23, 1145:4, 1198:10, 1198:15, 1198:23 <b>reasons</b> [5] - 1016:9, 1016:11, 1141:8, 1177:17, 1223:22 <b>rebuttal</b> [6] - 1120:10, 1120:12, 1123:13, 1123:15, 1124:6, 1156:12 <b>recalculate</b> [3] - 1121:16, 1122:10, 1124:1 <b>recalling</b> [1] - 1239:25 <b>receive</b> [1] - 1165:17 <b>received</b> [3] - 1027:25, 1028:1, 1163:17 <b>recent</b> [1] - 1028:1 <b>recently</b> [2] - 1029:25, 1259:23 <b>receptive</b> [1] - 1125:24 <b>receptor</b> [2] - 1048:6, 1110:11 <b>Receptor</b> [2] - 1072:5, 1159:24 <b>receptors</b> [13] - 1035:12, 1035:13, 1037:13, 1040:17, 1107:13, 1107:16, 1107:21, 1108:2, 1110:3, 1110:4, 1110:16, 1157:23, 1210:3 <b>recess</b> [1] - 1207:13 <b>Recess</b> [1] - 1126:9 <b>reciprocal</b> [1] - 1135:14	<b>recite</b> [2] - 1174:25, 1229:2 <b>recognize</b> [6] - 1034:16, 1036:18, 1037:21, 1071:18, 1204:25, 1257:17 <b>recognized</b> [1] - 1043:16 <b>recollect</b> [1] - 1213:18 <b>recollection</b> [7] - 1086:22, 1087:1, 1088:3, 1089:21, 1143:22, 1239:22, 1257:18 <b>recombinant</b> [12] - 1081:8, 1081:12, 1082:2, 1083:6, 1083:20, 1085:14, 1100:12, 1100:14, 1100:18, 1128:9, 1131:2, 1141:11 <b>recommendation</b> [3] - 1050:8, 1050:10, 1101:2 <b>Recommendations</b> [1] - 1094:7 <b>recommendations</b> [4] - 1050:5, 1090:18, 1143:13, 1153:16 <b>recommended</b> [5] - 1148:8, 1173:17, 1183:21, 1211:11, 1217:23 <b>reconvene</b> [1] - 1257:16 <b>record</b> [23] - 1014:4, 1014:22, 1025:12, 1042:16, 1043:21, 1043:25, 1080:10, 1123:17, 1154:19, 1155:3, 1157:7, 1211:18, 1226:11, 1234:8, 1259:21, 1261:12, 1263:9, 1267:3, 1268:14, 1268:21, 1269:4, 1269:5, 1271:12 <b>recording</b> [1] - 1179:5 <b>recumbent</b> [2] - 1104:25, 1136:21 <b>recumbently</b> [1] - 1066:4 <b>REDIRECT</b> [2] - 1116:6, 1214:13 <b>redirect</b> [13] - 1014:2, 1018:4, 1018:7, 1018:12, 1068:12, 1116:4, 1161:23, 1162:4, 1206:1, 1206:8, 1206:9,
---	--	--	---	--

<p>1214:12, 1221:16  <b>reduce</b> [4] - 1046:17,  1135:12, 1178:10,  1234:21  <b>reduced</b> [2] - 1047:4,  1140:11  <b>reducing</b> [25] -  1007:12, 1020:13,  1021:3, 1021:8,  1185:9, 1226:23,  1234:10, 1234:24,  1235:14, 1236:5,  1236:19, 1237:8,  1237:12, 1243:8,  1249:25, 1250:7,  1250:9, 1250:13,  1251:1, 1254:16,  1255:10, 1255:14,  1255:25, 1270:19  <b>refer</b> [4] - 1155:8,  1191:10, 1232:10,  1234:11  <b>Reference</b> [1] -  1039:19  <b>reference</b> [65] -  1006:12, 1006:18,  1009:15, 1015:22,  1015:24, 1032:9,  1032:12, 1032:14,  1039:14, 1039:20,  1040:3, 1042:17,  1042:18, 1045:6,  1049:11, 1049:15,  1049:17, 1049:23,  1051:4, 1051:6,  1051:12, 1052:25,  1053:19, 1053:20,  1054:4, 1054:12,  1054:17, 1055:6,  1055:7, 1055:12,  1055:19, 1055:22,  1055:25, 1056:14,  1056:23, 1056:25,  1057:12, 1057:20,  1057:23, 1058:19,  1058:23, 1062:17,  1062:18, 1062:21,  1062:25, 1063:1,  1063:4, 1066:17,  1069:18, 1070:16,  1070:19, 1071:3,  1071:13, 1071:19,  1108:12, 1108:15,  1129:18, 1151:1,  1151:11, 1160:17,  1160:21, 1182:19,  1189:24, 1190:12  <b>references</b> [13] -  1039:17, 1043:8,  1047:7, 1047:13,</p>	<p>1047:15, 1052:19,  1052:23, 1056:20,  1056:22, 1057:3,  1057:7, 1057:19,  1184:7  <b>referred</b> [3] - 1080:9,  1128:5, 1198:18  <b>referring</b> [5] - 1066:6,  1087:17, 1091:4,  1092:25, 1130:5  <b>refers</b> [4] - 1036:9,  1070:21, 1166:4,  1240:20  <b>reflected</b> [1] - 1046:1  <b>reflects</b> [2] - 1014:22,  1143:16  <b>refresh</b> [3] - 1086:22,  1088:2, 1143:22  <b>refreshing</b> [2] -  1087:1, 1089:20  <b>regard</b> [1] - 1103:12  <b>Regard</b> [1] - 1070:9  <b>regarded</b> [4] -  1069:20, 1069:25,  1070:3, 1103:10  <b>regarding</b> [4] -  1125:1, 1172:24,  1234:18, 1271:17  <b>regardless</b> [1] -  1204:17  <b>regards</b> [1] - 1130:8  <b>regimen</b> [1] - 1091:18  <b>regimented</b> [1] -  1179:22  <b>registration</b> [3] -  1186:16, 1198:19,  1198:22  <b>regular</b> [1] - 1179:7  <b>regulated</b> [1] -  1259:16  <b>regulations</b> [1] -  1013:15  <b>regulatory</b> [3] -  1010:7, 1011:21,  1013:8  <b>reinvent</b> [1] - 1260:6  <b>reissued</b> [8] -  1180:10, 1184:12,  1191:4, 1223:23,  1224:14, 1227:3,  1227:4, 1227:11  <b>related</b> [4] - 1037:6,  1143:18, 1181:17,  1213:14  <b>relates</b> [2] - 1026:25,  1029:7  <b>relation</b> [1] - 1106:5  <b>relationship</b> [3] -  1069:13, 1107:2,  1212:20</p>	<p><b>relative</b> [17] - 1081:15,  1081:18, 1081:21,  1081:24, 1082:3,  1084:14, 1131:10,  1131:20, 1131:24,  1132:2, 1132:9,  1132:13, 1132:15,  1134:3, 1134:6,  1134:9, 1155:4  <b>release</b> [1] - 1185:7  <b>released</b> [1] - 1203:4  <b>relevant</b> [7] - 1033:16,  1056:11, 1084:15,  1142:9, 1164:9,  1239:6, 1239:8  <b>reliable</b> [2] - 1141:12,  1264:6  <b>relied</b> [5] - 1011:17,  1044:4, 1049:12,  1072:21, 1169:22  <b>rely</b> [9] - 1036:22,  1042:19, 1047:6,  1072:24, 1073:2,  1136:8, 1137:5,  1220:23, 1239:10  <b>relying</b> [1] - 1239:13  <b>remain</b> [2] - 1006:6,  1165:5  <b>remaining</b> [2] -  1007:22, 1030:24  <b>remember</b> [8] -  1061:13, 1085:1,  1144:2, 1193:11,  1203:24, 1254:21,  1261:8, 1265:11  <b>remind</b> [4] - 1071:2,  1102:25, 1158:7,  1215:23  <b>reminded</b> [1] - 1162:1  <b>remote</b> [1] - 1102:4  <b>remove</b> [1] - 1022:19  <b>renal</b> [1] - 1133:4  <b>render</b> [1] - 1184:12  <b>renew</b> [1] - 1221:22  <b>renewable</b> [1] -  1213:19  <b>renewed</b> [3] -  1213:16, 1213:21,  1225:13  <b>reoccurs</b> [1] - 1247:13  <b>repeat</b> [3] - 1017:17,  1146:17, 1197:3  <b>repeatedly</b> [1] -  1183:15  <b>repetition</b> [1] -  1141:12  <b>reply</b> [7] - 1120:22,  1266:9, 1266:20,  1267:6, 1269:7,  1269:10, 1269:17</p>	<p><b>report</b> [4] - 1130:3,  1156:12, 1167:12,  1178:2  <b>reported</b> [1] - 1021:24  <b>Reporter</b> [1] - 1035:21  <b>reporter</b> [6] - 1058:18,  1065:4, 1089:2,  1113:1, 1137:18,  1271:8  <b>REPORTER</b> [1] -  1089:4  <b>REPORTER'S</b> [1] -  1006:3  <b>reporters</b> [1] -  1269:25  <b>reports</b> [2] - 1110:21,  1149:2  <b>represent</b> [3] -  1024:13, 1043:25,  1261:12  <b>representative</b> [1] -  1042:14  <b>represents</b> [1] -  1133:8  <b>reproduction</b> [1] -  1199:20  <b>request</b> [2] - 1085:11,  1223:24  <b>require</b> [14] - 1020:15,  1033:20, 1050:14,  1087:18, 1195:10,  1195:15, 1197:16,  1197:17, 1198:4,  1198:6, 1243:6,  1255:6, 1264:2,  1269:21  <b>required</b> [11] -  1033:21, 1056:19,  1057:4, 1087:24,  1093:23, 1159:9,  1179:6, 1179:13,  1179:15, 1198:15,  1198:16  <b>requirement</b> [5] -  1012:2, 1012:22,  1055:21, 1144:12,  1223:2  <b>requirements</b> [8] -  1009:1, 1143:9,  1143:13, 1143:15,  1143:24, 1144:13,  1259:17, 1263:20  <b>requires</b> [7] - 1033:2,  1080:17, 1193:19,  1196:6, 1255:8,  1255:13, 1270:18  <b>requiring</b> [2] -  1193:16, 1248:16  <b>reread</b> [1] - 1193:6  <b>research</b> [8] -</p>	<p>1027:23, 1027:25,  1047:19, 1128:23,  1152:25, 1153:8,  1163:23, 1163:24  <b>reserve</b> [2] - 1225:25,  1226:12  <b>reserved</b> [1] - 1268:13  <b>reset</b> [6] - 1089:7,  1164:15, 1165:16,  1177:19, 1182:14,  1183:8  <b>resetting</b> [4] -  1163:25, 1164:13,  1175:9, 1175:20  <b>residential</b> [1] -  1187:3  <b>resort</b> [4] - 1238:8,  1238:11, 1243:5,  1245:10  <b>respect</b> [22] - 1020:18,  1060:12, 1062:20,  1069:25, 1070:3,  1071:3, 1097:3,  1100:3, 1100:14,  1101:22, 1102:10,  1112:6, 1129:20,  1165:16, 1174:13,  1188:4, 1189:8,  1217:11, 1227:13,  1266:5, 1269:15,  1271:7  <b>respond</b> [3] - 1265:8,  1266:3  <b>response</b> [28] -  1120:11, 1168:18,  1168:23, 1170:9,  1170:12, 1170:13,  1171:2, 1171:8,  1171:11, 1172:10,  1172:13, 1172:16,  1173:5, 1173:10,  1173:18, 1173:21,  1173:22, 1175:17,  1177:5, 1177:15,  1178:5, 1180:22,  1183:5, 1183:17,  1199:15, 1266:8  <b>responses</b> [3] -  1014:8, 1022:25,  1172:20  <b>responsible</b> [4] -  1049:20, 1097:14,  1097:23, 1134:1  <b>rest</b> [6] - 1066:22,  1067:1, 1069:23,  1101:17, 1215:16,  1221:17  <b>restricted</b> [1] -  1164:20  <b>result</b> [9] - 1034:8,</p>
---	--	--	---	--

<p>1042:6, 1078:15, 1118:16, 1131:6, 1134:19, 1141:19, 1150:5, 1252:11 <b>results</b> [7] - 1047:3, 1098:15, 1098:16, 1098:20, 1118:14, 1127:9, 1159:7 <b>resuming</b> [2] - 1120:12, 1120:15 <b>retainer</b> [1] - 1213:7 <b>reverse</b> [1] - 1117:23 <b>review</b> [14] - 1034:19, 1038:8, 1038:21, 1042:12, 1054:25, 1063:14, 1064:9, 1113:25, 1146:9, 1146:25, 1219:4, 1269:24, 1270:2 <b>reviewed</b> [3] - 1062:10, 1062:14, 1219:2 <b>reviewer's</b> [1] - 1063:11 <b>reviewing</b> [1] - 1044:2 <b>rhythm</b> [10] - 1062:6, 1163:1, 1164:2, 1165:17, 1167:20, 1178:1, 1184:22, 1192:1, 1201:19, 1202:20 <b>rhythms</b> [2] - 1163:1, 1201:1 <b>Rifampicin</b> [1] - 1043:14 <b>rifampicin</b> [7] - 1129:15, 1140:12, 1148:20, 1148:23, 1151:22, 1151:25, 1154:8 <b>rifampin</b> [19] - 1029:3, 1046:6, 1046:12, 1046:20, 1047:5, 1048:3, 1048:17, 1050:24, 1050:25, 1051:1, 1051:19, 1051:24, 1104:10, 1105:11, 1116:15, 1117:2, 1117:11, 1129:14, 1161:19 <b>rifampicin</b> [2] - 1060:15, 1060:19 <b>RIFKIND</b> [1] - 1005:8 <b>right-hand</b> [4] - 1049:5, 1151:10, 1161:9, 1200:3 <b>rigorous</b> [2] - 1218:4, 1262:12 <b>ring</b> [3] - 1157:19, 1157:21, 1204:22</p>	<p><b>rise</b> [1] - 1224:11 <b>risen</b> [1] - 1177:12 <b>rising</b> [3] - 1044:20, 1176:16, 1177:10 <b>risk</b> [3] - 1077:17, 1101:11, 1236:20 <b>Robert</b> [1] - 1208:12 <b>role</b> [6] - 1040:24, 1073:9, 1106:1, 1112:7, 1116:19, 1128:1 <b>Rolfe</b> [2] - 2:1, 1272:7 <b>room</b> [1] - 1267:9 <b>rose</b> [3] - 1176:9, 1177:2, 1194:8 <b>rotation</b> [2] - 1021:22, 1264:7 <b>rough</b> [2] - 1269:25, 1270:4 <b>round</b> [2] - 1120:13, 1216:1 <b>rounds</b> [1] - 1266:2 <b>routine</b> [1] - 1033:22 <b>routinely</b> [2] - 1152:24, 1153:7 <b>row</b> [1] - 1135:6 <b>rows</b> [1] - 1135:4 <b>Rozendaal</b> [14] - 1006:5, 1015:5, 1019:22, 1020:7, 1124:5, 1190:19, 1203:12, 1205:8, 1207:6, 1214:16, 1225:21, 1228:22, 1249:8, 1258:20 <b>rozendaal</b> [2] - 1122:19, 1126:1 <b>ROZENDAAL</b> [76] - 1005:3, 1006:8, 1013:25, 1014:9, 1014:14, 1014:20, 1015:6, 1015:13, 1016:23, 1018:20, 1020:2, 1024:20, 1024:25, 1122:21, 1123:15, 1123:19, 1124:7, 1126:2, 1126:5, 1163:3, 1165:9, 1169:11, 1170:1, 1171:24, 1185:21, 1190:18, 1191:20, 1191:24, 1205:10, 1205:14, 1205:18, 1206:1, 1206:4, 1206:17, 1207:9, 1207:14, 1207:24, 1208:1, 1209:4, 1209:7, 1209:13, 1209:18, 1210:11, 1211:19,</p>	<p>1214:10, 1221:18, 1221:21, 1225:22, 1227:14, 1228:8, 1249:10, 1249:16, 1250:4, 1250:8, 1250:12, 1250:15, 1250:20, 1250:24, 1253:14, 1253:17, 1253:21, 1253:23, 1254:3, 1254:6, 1254:10, 1254:19, 1257:20, 1258:21, 1258:25, 1260:14, 1265:13, 1267:7, 1268:8, 1270:23, 1271:5, 1271:15 <b>Rozendaal's</b> [1] - 1014:23 <b>Rozerem</b> [3] - 1029:19, 1036:21, 1047:4 <b>RPR</b> [2] - 2:1, 1272:7 <b>Rudiger</b> [2] - 1061:23, 1061:24 <b>Rugby</b> [2] - 1221:6, 1221:10 <b>Rule</b> [3] - 1017:22, 1087:19, 1226:6 <b>rule</b> [2] - 1113:5, 1124:21 <b>rules</b> [2] - 1087:24, 1088:6 <b>ruling</b> [2] - 1226:1, 1256:25 <b>run</b> [10] - 1024:12, 1100:14, 1127:3, 1128:13, 1131:1, 1141:23, 1148:16, 1200:1, 1235:19, 1271:3 <b>running</b> [2] - 1082:19, 1171:5</p>	<p>1195:10, 1196:18 <b>sandwiches</b> [1] - 1206:20 <b>SAR</b> [2] - 1106:23, 1107:1 <b>satisfied</b> [1] - 1087:19 <b>satisfy</b> [1] - 1260:4 <b>satisfying</b> [1] - 1198:3 <b>saw</b> [10] - 1037:12, 1074:6, 1141:19, 1147:17, 1186:24, 1192:15, 1218:11, 1225:16, 1232:24 <b>scale</b> [4] - 1044:15, 1186:13, 1219:22, 1262:14 <b>schedule</b> [4] - 1170:24, 1179:7, 1265:19, 1269:7 <b>schematic</b> [5] - 1030:10, 1133:9, 1199:15, 1199:20, 1200:14 <b>scheme</b> [10] - 1235:7, 1236:10, 1236:12, 1237:17, 1243:13, 1243:14, 1243:15, 1254:9, 1254:10, 1256:10 <b>School</b> [6] - 1025:22, 1026:14, 1026:20, 1163:11, 1163:17, 1163:21 <b>school</b> [2] - 1164:22, 1187:3 <b>Science</b> [1] - 1165:19 <b>scientific</b> [10] - 1027:17, 1036:16, 1042:4, 1043:7, 1043:17, 1113:6, 1119:5, 1213:2, 1213:5, 1234:7 <b>scientists</b> [3] - 1076:17, 1113:8, 1180:24 <b>scope</b> [2] - 1158:4, 1158:13 <b>score</b> [1] - 1077:5 <b>screen</b> [7] - 1027:8, 1027:24, 1088:20, 1149:10, 1170:5, 1191:21, 1199:14 <b>screening</b> [1] - 1080:17 <b>scrivener</b> [1] - 1244:1 <b>search</b> [1] - 1233:22 <b>seat</b> [2] - 1126:10, 1269:3 <b>seated</b> [1] - 1258:12 <b>second</b> [18] - 1015:11,</p>	<p>1023:8, 1031:13, 1038:24, 1055:20, 1069:4, 1081:12, 1082:5, 1086:11, 1121:15, 1123:1, 1123:2, 1129:13, 1131:19, 1135:11, 1172:3, 1255:10, 1266:21 <b>second-to-last</b> [2] - 1123:1, 1123:2 <b>secondary</b> [2] - 1063:18, 1063:20 <b>secondly</b> [1] - 1263:24 <b>seconds</b> [1] - 1122:16 <b>section</b> [14] - 1039:17, 1046:3, 1064:6, 1064:11, 1068:23, 1106:23, 1109:7, 1109:12, 1113:15, 1115:8, 1115:14, 1152:15, 1263:1 <b>sections</b> [1] - 1108:25 <b>see</b> [114] - 1007:6, 1012:12, 1018:17, 1023:1, 1025:25, 1031:23, 1032:10, 1039:15, 1044:20, 1047:13, 1050:2, 1061:20, 1062:7, 1062:8, 1064:4, 1066:19, 1067:6, 1068:13, 1068:19, 1068:20, 1069:11, 1069:15, 1070:12, 1072:6, 1074:2, 1074:12, 1074:14, 1074:15, 1085:13, 1088:16, 1090:4, 1094:8, 1094:11, 1096:2, 1096:15, 1096:16, 1097:16, 1100:13, 1102:21, 1106:24, 1107:14, 1107:24, 1108:4, 1112:22, 1112:23, 1113:13, 1114:22, 1115:1, 1115:10, 1115:14, 1115:25, 1125:24, 1130:5, 1131:22, 1135:13, 1135:14, 1135:25, 1140:10, 1140:13, 1144:16, 1147:23, 1148:4, 1149:18, 1149:24, 1150:1, 1150:8, 1150:13, 1150:21, 1151:11, 1151:16, 1152:15, 1152:17, 1152:22,</p>
<b>S</b>				
	<p><b>Sack</b> [2] - 1173:9, 1208:12 <b>safe</b> [5] - 1139:11, 1186:14, 1203:9, 1209:23, 1263:19 <b>safeguards</b> [2] - 1118:23, 1119:19 <b>safely</b> [3] - 1042:3, 1117:7, 1118:9 <b>safer</b> [1] - 1047:20 <b>safety</b> [1] - 1118:17 <b>sake</b> [1] - 1231:11 <b>sample</b> [2] - 1057:11, 1208:14 <b>samples</b> [3] - 1134:14,</p>			

1153:5, 1153:10, 1153:17, 1153:19, 1153:25, 1154:4, 1158:2, 1158:3, 1158:22, 1158:25, 1159:5, 1159:21, 1160:2, 1160:4, 1160:7, 1160:15, 1160:16, 1160:18, 1160:22, 1161:6, 1161:10, 1161:12, 1161:20, 1166:9, 1186:25, 1191:11, 1192:5, 1192:6, 1199:14, 1203:10, 1219:4, 1224:8, 1227:17, 1230:10, 1234:1, 1234:2, 1245:2, 1257:7, 1259:5, 1266:7, 1268:16 <b>seeing</b> [7] - 1046:19, 1103:21, 1114:10, 1138:17, 1139:5, 1139:6, 1259:6 <b>seem</b> [3] - 1112:14, 1154:24, 1242:20 <b>seize</b> [1] - 1103:23 <b>semicolon</b> [1] - 1255:19 <b>sends</b> [1] - 1203:1 <b>senior</b> [1] - 1163:20 <b>sense</b> [8] - 1054:19, 1055:2, 1217:24, 1248:25, 1254:6, 1255:21, 1265:20, 1265:23 <b>sensing</b> [1] - 1112:19 <b>sensitive</b> [1] - 1045:20 <b>sent</b> [1] - 1182:18 <b>sentence</b> [12] - 1067:1, 1068:18, 1070:21, 1074:4, 1103:24, 1109:7, 1147:21, 1150:10, 1160:25, 1161:10, 1208:22, 1230:3 <b>separate</b> [4] - 1217:20, 1251:13, 1263:8, 1269:1 <b>separately</b> [1] - 1241:18 <b>sequential</b> [11] - 1230:11, 1231:2, 1231:13, 1236:25, 1237:1, 1237:18, 1238:2, 1238:24, 1239:21, 1248:17, 1255:11 <b>sequestered</b> [1] -	1018:24 <b>series</b> [3] - 1208:13, 1233:3 <b>serve</b> [1] - 1219:18 <b>served</b> [4] - 1026:18, 1027:5, 1027:13, 1027:18 <b>Service</b> [1] - 1026:16 <b>services</b> [3] - 1126:25, 1212:22, 1213:6 <b>set</b> [12] - 1020:19, 1021:9, 1129:3, 1151:19, 1173:22, 1180:10, 1196:13, 1255:18, 1256:8, 1265:12, 1265:13, 1269:18 <b>SET</b> [1] - 1182:14 <b>sets</b> [1] - 1217:19 <b>seven</b> [5] - 1148:9, 1148:14, 1187:2, 1208:20, 1234:16 <b>several</b> [7] - 1107:21, 1172:12, 1190:23, 1240:10, 1257:19, 1259:21, 1261:5 <b>shape</b> [2] - 1106:7, 1170:22 <b>share</b> [3] - 1108:10, 1135:10, 1156:17 <b>sharp</b> [1] - 1189:21 <b>SHAW</b> [1] - 1005:2 <b>shielded</b> [1] - 1170:14 <b>shift</b> [9] - 1140:2, 1166:21, 1175:15, 1175:16, 1177:4, 1177:15, 1178:1, 1178:3, 1200:18 <b>shifted</b> [1] - 1179:12 <b>shifting</b> [5] - 1177:5, 1181:5, 1201:24, 1202:8, 1204:15 <b>shifts</b> [1] - 1203:13 <b>short</b> [5] - 1040:17, 1040:19, 1118:6, 1123:10, 1189:21 <b>shorten</b> [2] - 1125:24, 1201:2 <b>shorter</b> [1] - 1123:8 <b>shortest</b> [1] - 1267:25 <b>shortly</b> [3] - 1201:17, 1271:17, 1271:19 <b>show</b> [13] - 1087:25, 1101:18, 1117:19, 1119:12, 1135:22, 1164:14, 1173:1, 1195:17, 1198:15, 1198:23, 1259:1 <b>showed</b> [2] - 1138:2, 1259:25	<b>showing</b> [12] - 1030:6, 1044:14, 1046:15, 1064:16, 1130:1, 1131:5, 1132:23, 1132:25, 1137:23, 1173:5, 1217:14 <b>shown</b> [17] - 1049:5, 1066:18, 1066:19, 1114:8, 1146:15, 1146:21, 1172:13, 1173:3, 1175:8, 1177:19, 1181:4, 1184:24, 1185:1, 1208:10, 1208:16, 1208:17, 1223:14 <b>shows</b> [5] - 1031:9, 1119:6, 1170:9, 1173:4, 1252:16 <b>side</b> [13] - 1014:17, 1017:21, 1049:6, 1056:7, 1068:23, 1101:23, 1200:3, 1207:3, 1216:10, 1216:13, 1249:14, 1268:24, 1269:10 <b>sidebar</b> [8] - 1014:19, 1014:21, 1014:24, 1015:3, 1019:6, 1054:6, 1054:9, 1058:14 <b>sides</b> [5] - 1016:16, 1112:14, 1112:16, 1154:25, 1245:2 <b>sighted</b> [7] - 1164:18, 1164:25, 1167:2, 1170:13, 1175:11, 1199:23, 1202:3 <b>signals</b> [1] - 1041:18 <b>significance</b> [7] - 1055:14, 1056:10, 1056:13, 1056:18, 1173:25, 1232:20, 1264:25 <b>significant</b> [6] - 1045:23, 1105:13, 1148:2, 1153:22, 1155:25, 1229:4 <b>significantly</b> [2] - 1011:6, 1214:6 <b>silly</b> [1] - 1015:2 <b>similar</b> [7] - 1037:12, 1040:21, 1046:10, 1103:24, 1108:13, 1109:8, 1135:25 <b>similarities</b> [1] - 1048:5 <b>similarity</b> [5] - 1104:18, 1104:19, 1108:9, 1108:16, 1157:9	<b>similarly</b> [1] - 1189:8 <b>simple</b> [1] - 1181:20 <b>simply</b> [8] - 1022:9, 1022:16, 1101:12, 1101:23, 1189:4, 1231:18, 1237:14, 1243:22 <b>simulate</b> [1] - 1175:13 <b>simultaneous</b> [5] - 1231:3, 1231:13, 1238:25, 1243:7, 1248:16 <b>simultaneously</b> [5] - 1239:9, 1247:16, 1255:14, 1266:3, 1270:20 <b>Singh</b> [1] - 1009:15 <b>single</b> [9] - 1031:17, 1053:4, 1057:11, 1062:21, 1063:9, 1070:17, 1133:14, 1133:22, 1254:12 <b>single-spaced</b> [1] - 1063:9 <b>site</b> [2] - 1104:20, 1107:18 <b>sitting</b> [2] - 1164:4, 1241:14 <b>situate</b> [1] - 1106:15 <b>situation</b> [5] - 1019:10, 1041:4, 1168:7, 1244:17, 1245:3 <b>six</b> [17] - 1031:21, 1031:23, 1067:6, 1074:6, 1074:10, 1148:1, 1173:19, 1174:5, 1208:21, 1230:2, 1232:9, 1242:11, 1243:15, 1243:19, 1243:21, 1243:25, 1266:11 <b>sixth</b> [2] - 1208:3, 1256:20 <b>size</b> [2] - 1052:1, 1173:15 <b>skill</b> [53] - 1007:24, 1008:21, 1010:21, 1011:20, 1012:4, 1012:12, 1012:17, 1013:7, 1015:18, 1023:13, 1024:18, 1028:17, 1029:7, 1029:8, 1032:24, 1043:10, 1045:16, 1048:12, 1049:12, 1049:24, 1050:7, 1050:14, 1051:4, 1053:6, 1059:15, 1062:17, 1064:8,	1066:16, 1069:8, 1070:2, 1072:13, 1072:15, 1100:5, 1103:21, 1104:8, 1104:15, 1116:13, 1116:25, 1145:3, 1145:22, 1146:4, 1146:13, 1146:19, 1147:8, 1148:19, 1149:4, 1156:2, 1156:7, 1173:20, 1177:16, 1180:25, 1198:10, 1238:12 <b>skilled</b> [35] - 1054:3, 1056:24, 1060:4, 1060:8, 1060:13, 1060:17, 1061:7, 1061:8, 1061:11, 1068:24, 1069:7, 1074:11, 1092:8, 1092:12, 1092:18, 1098:2, 1101:9, 1101:21, 1102:9, 1104:4, 1105:4, 1109:15, 1111:20, 1129:17, 1130:7, 1132:2, 1134:9, 1134:18, 1135:7, 1138:13, 1140:20, 1141:5, 1171:9, 1177:7, 1236:15 <b>skin</b> [1] - 1138:22 <b>slam</b> [1] - 1268:11 <b>sleep</b> [80] - 1030:1, 1037:8, 1062:6, 1110:3, 1163:1, 1164:2, 1164:20, 1164:22, 1165:1, 1165:4, 1165:6, 1165:22, 1166:6, 1166:17, 1166:18, 1166:19, 1166:20, 1166:22, 1166:24, 1167:4, 1167:7, 1167:10, 1167:13, 1167:18, 1167:19, 1167:20, 1167:21, 1167:22, 1167:25, 1168:1, 1168:4, 1168:5, 1168:6, 1168:9, 1168:12, 1168:15, 1170:24, 1173:7, 1175:11, 1178:24, 1179:6, 1183:4, 1183:20, 1183:23, 1184:1, 1190:1, 1190:4, 1190:6, 1191:5, 1191:9, 1192:2, 1192:15, 1192:17, 1194:17, 1196:10,
---	---	---	---	---



<p>1196:13, 1197:10, 1201:17, 1202:20, 1202:24, 1203:5, 1203:7, 1203:9, 1203:16, 1203:17, 1203:20, 1212:7, 1217:16, 1217:23, 1220:7, 1220:10, 1227:2, 1227:10, 1227:16, 1228:1, 1228:8, 1228:9, 1239:24 <b>Sleep</b> [5] - 1163:9, 1163:11, 1163:12, 1192:4, 1217:19 <b>sleep-wake</b> [15] - 1167:21, 1168:6, 1170:24, 1179:6, 1184:1, 1191:5, 1191:9, 1192:15, 1192:17, 1194:17, 1196:13, 1197:10, 1203:16, 1220:7, 1220:10 <b>Sleep-Wake</b> [1] - 1192:4 <b>sleepiness</b> [1] - 1210:24 <b>sleeping</b> [3] - 1165:3, 1187:5, 1228:4 <b>sleepy</b> [1] - 1182:8 <b>slept</b> [1] - 1241:20 <b>slide</b> [34] - 1030:9, 1031:9, 1047:9, 1047:25, 1049:6, 1049:15, 1052:20, 1080:15, 1083:11, 1109:18, 1130:1, 1130:18, 1130:24, 1131:19, 1132:18, 1132:24, 1132:25, 1133:14, 1134:25, 1137:24, 1167:11, 1172:6, 1172:9, 1176:14, 1180:9, 1181:11, 1181:12, 1184:20, 1185:17, 1186:2, 1188:3, 1199:8, 1234:8, 1234:16 <b>Slide</b> [3] - 1166:11, 1166:13, 1172:7 <b>slides</b> [8] - 1129:3, 1166:7, 1199:8, 1202:19, 1225:5, 1228:14, 1238:6, 1249:13 <b>slightly</b> [1] - 1234:7 <b>slip</b> [5] - 1183:22, 1203:18, 1203:19,</p>	<p>1203:25, 1204:6 <b>slipped</b> [1] - 1144:19 <b>slips</b> [1] - 1203:14 <b>slower</b> [2] - 1041:13, 1205:11 <b>small</b> [15] - 1030:15, 1030:16, 1030:18, 1035:15, 1045:19, 1065:25, 1117:11, 1124:6, 1134:7, 1146:14, 1146:21, 1147:11, 1148:17, 1151:12, 1151:19 <b>small-molecule</b> [2] - 1146:21, 1147:11 <b>smaller</b> [1] - 1031:14 <b>smart</b> [1] - 1257:22 <b>smoking</b> [1] - 1161:18 <b>snack</b> [1] - 1185:10 <b>so-call</b> [1] - 1174:8 <b>so-called</b> [7] - 1035:16, 1041:8, 1119:2, 1168:17, 1181:6, 1188:16, 1228:21 <b>so...</b> [4] - 1124:21, 1187:25, 1267:10, 1268:16 <b>societies</b> [1] - 1027:17 <b>society</b> [1] - 1167:6 <b>sodium</b> [3] - 1020:12, 1020:16, 1021:5 <b>sold</b> [1] - 1223:16 <b>solubilized</b> [1] - 1030:14 <b>solution</b> [1] - 1249:18 <b>solve</b> [1] - 1053:10 <b>solvents</b> [1] - 1235:1 <b>solves</b> [1] - 1249:23 <b>someone</b> [4] - 1010:9, 1011:9, 1183:4, 1193:10 <b>sometimes</b> [10] - 1041:7, 1079:6, 1079:8, 1117:18, 1166:24, 1177:4, 1198:17, 1241:17, 1256:16 <b>somewhere</b> [4] - 1021:24, 1085:23, 1089:20, 1214:1 <b>soporific</b> [3] - 1182:6, 1190:2, 1211:3 <b>sorry</b> [29] - 1010:20, 1038:5, 1045:3, 1047:8, 1081:20, 1082:19, 1084:22, 1091:6, 1091:20, 1095:13, 1096:6, 1097:10, 1114:14,</p>	<p>1122:8, 1146:17, 1149:17, 1149:23, 1176:23, 1183:12, 1188:9, 1195:23, 1197:3, 1200:10, 1211:16, 1225:12, 1228:19, 1229:14, 1235:11, 1261:22 <b>sort</b> [8] - 1055:18, 1056:9, 1201:17, 1205:3, 1219:21, 1243:10, 1252:17, 1254:13 <b>sorts</b> [1] - 1225:20 <b>sought</b> [1] - 1207:20 <b>sound</b> [1] - 1055:20 <b>sounds</b> [2] - 1226:14 <b>source</b> [11] - 1053:4, 1063:18, 1063:20, 1063:21, 1073:8, 1074:11, 1075:2, 1075:4, 1130:11, 1258:4 <b>spaced</b> [1] - 1063:9 <b>speaking</b> [4] - 1038:19, 1045:15, 1062:20, 1216:13 <b>special</b> [3] - 1091:13, 1196:4, 1229:23 <b>specialist</b> [1] - 1212:8 <b>specialized</b> [1] - 1030:21 <b>specific</b> [16] - 1031:17, 1031:18, 1033:6, 1049:21, 1063:4, 1064:22, 1065:5, 1068:5, 1073:22, 1077:25, 1085:16, 1114:19, 1131:16, 1141:24, 1170:16, 1234:23 <b>specifically</b> [10] - 1012:3, 1027:1, 1067:10, 1110:10, 1168:18, 1186:5, 1224:14, 1229:8, 1233:19, 1270:17 <b>specification</b> [4] - 1189:25, 1190:8, 1229:7, 1234:16 <b>specifications</b> [1] - 1020:25 <b>specified</b> [2] - 1234:10, 1237:8 <b>specifies</b> [2] - 1235:2 <b>specify</b> [1] - 1155:23 <b>spectrum</b> [1] - 1150:11 <b>speed</b> [1] - 1235:4 <b>spell</b> [4] - 1035:20,</p>	<p>1065:3, 1137:17, 1243:15 <b>spelled</b> [2] - 1020:25, 1058:20 <b>spend</b> [1] - 1064:19 <b>spent</b> [1] - 1105:13 <b>spillover</b> [6] - 1174:22, 1174:23, 1175:18, 1176:18, 1199:1, 1199:4 <b>split</b> [2] - 1121:18, 1124:20 <b>sponsor</b> [4] - 1106:3, 1106:14, 1119:2, 1119:14 <b>sponte</b> [1] - 1227:19 <b>Squibb</b> [3] - 1036:15, 1072:9, 1211:11 <b>stage</b> [2] - 1084:15, 1089:8 <b>stand</b> [7] - 1017:8, 1019:2, 1019:18, 1215:19, 1233:22, 1239:12, 1256:25 <b>standard</b> [6] - 1022:17, 1033:1, 1094:1, 1133:19, 1143:16, 1206:18 <b>standards</b> [1] - 1017:23 <b>standing</b> [2] - 1101:22, 1224:22 <b>stands</b> [1] - 1031:10 <b>Stanford</b> [1] - 1163:16 <b>stark</b> [1] - 1076:9 <b>start</b> [32] - 1008:7, 1012:24, 1033:1, 1040:13, 1053:12, 1054:16, 1055:2, 1055:6, 1055:9, 1055:16, 1061:17, 1080:15, 1084:19, 1093:20, 1093:21, 1102:11, 1145:14, 1153:1, 1168:9, 1169:5, 1178:24, 1230:12, 1230:19, 1231:21, 1232:1, 1232:25, 1234:3, 1243:11, 1246:6, 1249:16, 1256:14, 1267:5 <b>started</b> [6] - 1168:5, 1177:10, 1178:11, 1186:10, 1215:5, 1228:17 <b>starting</b> [7] - 1006:11, 1051:1, 1054:24, 1091:8, 1097:18, 1167:22, 1205:3</p>	<p><b>starts</b> [3] - 1055:20, 1096:10, 1127:23 <b>state</b> [5] - 1007:4, 1025:12, 1116:19, 1116:20, 1142:11 <b>statement</b> [4] - 1070:5, 1086:22, 1087:12, 1108:14 <b>statements</b> [2] - 1116:10, 1140:21 <b>States</b> [4] - 1059:13, 1059:25, 1185:14, 1212:4 <b>STATES</b> [1] - 1:2 <b>states</b> [3] - 1151:11, 1160:11, 1219:23 <b>stating</b> [1] - 1039:3 <b>statue</b> [1] - 1249:2 <b>stay</b> [5] - 1102:7, 1165:7, 1166:22, 1166:23 <b>staying</b> [2] - 1068:21, 1168:1 <b>stenographic</b> [1] - 1272:5 <b>step</b> [13] - 1008:6, 1014:12, 1023:16, 1101:22, 1119:23, 1215:12, 1221:14, 1232:23, 1251:11, 1251:13, 1252:3, 1256:21, 1259:7 <b>stepped</b> [1] - 1225:11 <b>steps</b> [15] - 1006:18, 1007:16, 1007:22, 1007:25, 1008:18, 1009:4, 1009:6, 1009:21, 1232:2, 1232:9, 1232:11, 1233:4, 1234:19, 1241:4, 1251:9 <b>Steven</b> [1] - 1208:12 <b>stick</b> [2] - 1250:16, 1252:12 <b>sticking</b> [1] - 1249:19 <b>still</b> [15] - 1020:3, 1020:4, 1067:3, 1084:7, 1105:9, 1119:8, 1128:1, 1176:20, 1178:7, 1197:11, 1235:10, 1245:14, 1246:23, 1250:20, 1263:21 <b>stimulated</b> [3] - 1177:14, 1178:4, 1183:5 <b>stimulus</b> [4] - 1164:13, 1174:24, 1175:3, 1175:21 <b>stipulated</b> [1] - 1028:9</p>
--	---	--	---	---

<p><b>stipulation</b> [4] - 1162:25, 1269:14, 1271:11, 1271:16</p> <p><b>stock</b> [4] - 1213:23, 1214:1, 1214:5, 1214:7</p> <p><b>stomach</b> [2] - 1030:13, 1030:14</p> <p><b>stone</b> [5] - 1016:24, 1054:11, 1080:7, 1244:5, 1246:4</p> <p><b>Stone</b> [1] - 1052:9</p> <p><b>STONE</b> [119] - 1005:9, 1024:12, 1026:6, 1028:9, 1032:19, 1035:1, 1037:1, 1038:2, 1038:12, 1042:24, 1044:8, 1048:24, 1052:4, 1052:8, 1054:7, 1054:13, 1054:19, 1055:15, 1056:2, 1056:16, 1057:9, 1057:14, 1058:2, 1058:7, 1058:12, 1058:16, 1061:16, 1061:18, 1063:24, 1064:1, 1064:15, 1064:17, 1069:4, 1069:6, 1071:21, 1071:25, 1072:2, 1073:14, 1073:16, 1073:18, 1073:20, 1079:17, 1079:24, 1080:8, 1080:13, 1086:13, 1086:15, 1086:19, 1086:23, 1087:2, 1087:14, 1087:21, 1088:5, 1088:11, 1089:1, 1089:5, 1089:6, 1089:23, 1094:25, 1095:2, 1095:8, 1095:11, 1095:17, 1095:25, 1096:1, 1096:18, 1096:21, 1099:7, 1099:9, 1099:13, 1099:17, 1099:20, 1099:21, 1106:19, 1106:21, 1107:9, 1107:11, 1110:20, 1110:23, 1110:25, 1111:1, 1112:17, 1112:22, 1113:12, 1113:16, 1114:13, 1114:16, 1116:2, 1120:9, 1120:18, 1120:24, 1121:3, 1121:8, 1121:12, 1122:5,</p>	<p>1122:8, 1122:13, 1123:2, 1123:23, 1124:15, 1125:11, 1125:19, 1216:13, 1240:15, 1240:18, 1241:20, 1246:5, 1246:14, 1246:17, 1246:21, 1247:1, 1247:7, 1248:2, 1248:5, 1248:9, 1266:1, 1266:7, 1266:11, 1266:14</p> <p><b>stop</b> [3] - 1066:8, 1072:16, 1190:7</p> <p><b>story</b> [2] - 1081:22, 1090:13</p> <p><b>stream</b> [1] - 1175:4</p> <p><b>stress</b> [2] - 1268:17, 1268:18</p> <p><b>stressful</b> [1] - 1162:13</p> <p><b>strict</b> [2] - 1218:5</p> <p><b>strike</b> [3] - 1102:7, 1158:14, 1158:17</p> <p><b>strikingly</b> [1] - 1251:24</p> <p><b>strong</b> [16] - 1028:24, 1043:11, 1047:4, 1049:8, 1051:19, 1060:15, 1100:15, 1102:22, 1105:11, 1138:8, 1148:20, 1148:24, 1149:5, 1161:17, 1161:18, 1237:10</p> <p><b>stronger</b> [2] - 1203:1</p> <p><b>strongest</b> [3] - 1043:3, 1043:6, 1043:15</p> <p><b>strongly</b> [1] - 1217:11</p> <p><b>struck</b> [1] - 1017:8</p> <p><b>structural</b> [5] - 1108:9, 1108:16, 1157:8, 1233:16, 1251:7</p> <p><b>structurally</b> [3] - 1103:24, 1108:13, 1109:8</p> <p><b>structure</b> [11] - 1040:20, 1048:6, 1104:20, 1107:2, 1107:6, 1109:5, 1109:7, 1156:17, 1158:9, 1251:13, 1251:16</p> <p><b>structures</b> [3] - 1040:11, 1040:22, 1259:19</p> <p><b>stuck</b> [3] - 1245:23, 1251:18, 1258:9</p> <p><b>students</b> [1] - 1063:19</p> <p><b>studied</b> [1] - 1202:4</p> <p><b>Studies</b> [3] - 1094:5,</p>	<p>1115:9, 1115:15</p> <p><b>studies</b> [29] - 1043:9, 1073:21, 1083:5, 1092:4, 1092:5, 1096:11, 1104:24, 1127:3, 1127:9, 1136:19, 1137:25, 1141:11, 1145:15, 1158:21, 1159:3, 1159:8, 1160:5, 1160:11, 1161:1, 1161:16, 1164:19, 1175:19, 1180:6, 1184:21, 1184:24, 1208:11, 1218:6, 1263:1</p> <p><b>study</b> [73] - 1026:22, 1034:9, 1036:9, 1039:22, 1046:10, 1064:21, 1064:24, 1065:2, 1065:24, 1066:6, 1067:24, 1076:17, 1077:16, 1077:18, 1077:19, 1077:22, 1084:14, 1084:17, 1085:14, 1086:2, 1090:3, 1104:5, 1105:2, 1106:3, 1108:22, 1128:6, 1128:9, 1128:10, 1128:11, 1128:13, 1129:19, 1130:6, 1130:11, 1131:1, 1131:13, 1132:10, 1134:8, 1134:11, 1135:22, 1137:15, 1138:1, 1138:11, 1139:14, 1140:23, 1141:15, 1141:16, 1141:20, 1142:9, 1143:18, 1144:22, 1145:2, 1154:15, 1158:25, 1159:1, 1169:20, 1173:9, 1173:12, 1173:14, 1174:21, 1178:2, 1184:25, 1185:15, 1186:15, 1195:12, 1199:2, 1202:3, 1211:12, 1264:16</p> <p><b>Study</b> [1] - 1094:6</p> <p><b>studying</b> [1] - 1032:24</p> <p><b>stuff</b> [3] - 1158:4, 1257:8, 1268:18</p> <p><b>sua</b> [1] - 1227:19</p> <p><b>sub</b> [1] - 1236:7</p> <p><b>subfamily</b> [1] - 1031:14</p> <p><b>subject</b> [11] - 1012:21,</p>	<p>1013:1, 1013:5, 1053:21, 1067:2, 1140:3, 1156:24, 1164:7, 1165:23, 1256:1, 1257:21</p> <p><b>subjects</b> [4] - 1044:19, 1134:12, 1175:12, 1218:6</p> <p><b>submission</b> [1] - 1106:8</p> <p><b>submit</b> [6] - 1265:21, 1270:2, 1270:7, 1271:2, 1271:4, 1271:14</p> <p><b>submitted</b> [6] - 1229:11, 1251:20, 1263:4, 1265:11, 1269:18, 1270:14</p> <p><b>subsequent</b> [4] - 1062:22, 1164:19, 1232:11, 1259:2</p> <p><b>subset</b> [1] - 1151:12</p> <p><b>substance</b> [1] - 1080:2</p> <p><b>substances</b> [2] - 1153:23, 1158:9</p> <p><b>substantial</b> [1] - 1085:22</p> <p><b>substrate</b> [8] - 1041:8, 1078:11, 1078:14, 1079:1, 1097:13, 1097:23, 1118:20, 1159:3</p> <p><b>substrates</b> [6] - 1078:5, 1078:21, 1099:24, 1100:14, 1141:18, 1188:23</p> <p><b>success</b> [9] - 1143:6, 1143:10, 1144:1, 1144:14, 1145:4, 1198:11, 1198:15, 1198:23, 1198:24</p> <p><b>successful</b> [3] - 1011:13, 1197:21, 1209:22</p> <p><b>successfully</b> [3] - 1152:25, 1153:9, 1218:16</p> <p><b>suddenly</b> [1] - 1175:12</p> <p><b>suffer</b> [2] - 1212:4</p> <p><b>suffering</b> [2] - 1196:8, 1199:24</p> <p><b>sufficient</b> [3] - 1206:22, 1270:20, 1270:21</p> <p><b>sufficiently</b> [1] - 1011:12</p> <p><b>sugar</b> [1] - 1185:7</p> <p><b>suggest</b> [7] - 1022:5,</p>	<p>1022:7, 1022:13, 1022:15, 1247:1, 1252:11, 1256:22</p> <p><b>suggested</b> [4] - 1066:7, 1160:11, 1161:1, 1214:22</p> <p><b>suggesting</b> [4] - 1049:13, 1051:5, 1083:14, 1083:15</p> <p><b>summarize</b> [2] - 1028:22, 1028:24</p> <p><b>summarized</b> [1] - 1170:21</p> <p><b>summarizing</b> [1] - 1031:8</p> <p><b>summary</b> [6] - 1040:6, 1047:23, 1099:2, 1099:3, 1131:6, 1137:25</p> <p><b>superb</b> [1] - 1082:21</p> <p><b>superfluous</b> [1] - 1230:6</p> <p><b>supersonic</b> [1] - 1179:16</p> <p><b>support</b> [1] - 1251:19</p> <p><b>supports</b> [1] - 1256:23</p> <p><b>suppose</b> [4] - 1196:24, 1197:4, 1221:21, 1266:9</p> <p><b>suprachiasmatic</b> [1] - 1107:17</p> <p><b>surely</b> [1] - 1052:2</p> <p><b>surety</b> [1] - 1259:10</p> <p><b>surge</b> [1] - 1203:11</p> <p><b>surprise</b> [2] - 1164:24, 1210:15</p> <p><b>surprised</b> [2] - 1111:9, 1182:24</p> <p><b>surprisingly</b> [1] - 1016:6</p> <p><b>susceptible</b> [1] - 1246:11</p> <p><b>suspect</b> [4] - 1024:3, 1060:18, 1224:16, 1266:4</p> <p><b>suspected</b> [1] - 1232:14</p> <p><b>sustain</b> [2] - 1158:3, 1158:6</p> <p><b>swapped</b> [1] - 1184:2</p> <p><b>switch</b> [1] - 1084:11</p> <p><b>sworn</b> [2] - 1126:13, 1215:21</p> <p><b>synchronization</b> [1] - 1193:19</p> <p><b>synchronize</b> [5] - 1187:25, 1193:10, 1193:20, 1194:2, 1194:11</p> <p><b>synchronized</b> [4] -</p>
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<p>1194:4, 1194:5, 1194:7</p> <p><b>synchronizing</b> [5] - 1170:18, 1192:9, 1192:16, 1193:15, 1193:17</p> <p><b>synonymous</b> [3] - 1192:21, 1193:21, 1193:22</p> <p><b>synonyms</b> [5] - 1074:24, 1074:25, 1240:22, 1241:4, 1241:17</p> <p><b>synthesis</b> [2] - 1006:22, 1010:19</p> <p><b>Synthesis</b> [1] - 1106:23</p> <p><b>system</b> [10] - 1076:24, 1081:19, 1132:18, 1174:25, 1177:20, 1183:14, 1194:20, 1219:17, 1219:25, 1220:11</p> <p><b>systematic</b> [2] - 1097:18, 1097:24</p> <p><b>systemic</b> [2] - 1097:15, 1111:15</p> <p><b>systems</b> [5] - 1145:23, 1145:25, 1157:19, 1157:21, 1219:22</p>	<p>1022:21, 1023:3, 1029:1, 1029:3, 1034:19, 1035:8, 1035:10, 1036:4, 1037:6, 1037:12, 1040:8, 1040:19, 1048:5, 1048:9, 1048:14, 1049:9, 1049:22, 1050:25, 1051:2, 1051:13, 1051:24, 1055:1, 1055:3, 1055:8, 1057:17, 1057:20, 1059:13, 1059:16, 1059:18, 1060:2, 1060:7, 1060:10, 1060:14, 1060:19, 1062:5, 1063:10, 1064:9, 1066:7, 1066:18, 1067:3, 1067:5, 1067:14, 1067:19, 1067:24, 1068:25, 1069:17, 1070:9, 1070:18, 1070:22, 1071:4, 1072:11, 1073:10, 1073:23, 1074:5, 1074:10, 1081:16, 1082:7, 1092:4, 1092:10, 1092:14, 1092:20, 1093:15, 1097:3, 1097:7, 1097:8, 1097:23, 1097:24, 1100:7, 1101:4, 1101:10, 1103:7, 1103:17, 1104:5, 1104:9, 1104:11, 1104:18, 1104:19, 1104:23, 1105:3, 1105:11, 1107:7, 1107:13, 1108:3, 1108:9, 1108:13, 1108:20, 1109:8, 1109:20, 1110:1, 1110:17, 1111:6, 1111:13, 1111:24, 1112:8, 1114:4, 1114:20, 1114:25, 1115:22, 1115:24, 1116:10, 1116:15, 1129:12, 1129:15, 1130:9, 1131:17, 1131:23, 1134:5, 1140:11, 1140:14, 1140:15, 1140:22, 1140:24, 1141:1, 1141:6, 1142:9, 1142:10, 1146:14, 1146:21, 1155:9, 1155:21, 1156:16, 1156:20,</p>	<p>1157:16, 1157:22, 1160:13, 1161:3, 1161:15, 1175:2, 1175:5, 1176:3, 1176:4, 1176:10, 1176:13, 1176:15, 1176:21, 1176:23, 1177:1, 1180:7, 1180:13, 1181:3, 1181:17, 1181:19, 1182:1, 1186:6, 1187:24, 1188:6, 1189:16, 1190:1, 1190:6, 1196:25, 1197:7, 1199:4, 1201:16, 1209:2, 1209:20, 1209:24, 1210:2, 1210:16, 1210:20, 1210:23, 1211:2, 1211:7, 1211:9, 1213:14, 1214:23, 1215:2, 1220:2, 1222:9, 1222:13, 1222:20, 1222:22, 1223:16, 1223:19, 1224:13, 1263:10</p> <p><b>tasimelton's</b> [2] - 1093:6, 1093:9</p> <p><b>task</b> [1] - 1217:20</p> <p><b>tau</b> [2] - 1200:23, 1201:2</p> <p><b>taught</b> [1] - 1172:23</p> <p><b>teach</b> [1] - 1063:19</p> <p><b>teacher</b> [1] - 1164:22</p> <p><b>teachers</b> [3] - 1187:4, 1187:8, 1187:9</p> <p><b>teaching</b> [5] - 1049:13, 1051:5, 1054:15, 1234:2</p> <p><b>teachings</b> [1] - 1012:5</p> <p><b>team</b> [3] - 1013:17, 1029:9, 1030:3</p> <p><b>teams</b> [1] - 1029:14</p> <p><b>tears</b> [1] - 1187:14</p> <p><b>technically</b> [2] - 1087:18, 1151:25</p> <p><b>technique</b> [1] - 1057:6</p> <p><b>techniques</b> [2] - 1065:16, 1115:21</p> <p><b>Technologies</b> [1] - 1252:21</p> <p><b>ten</b> [2] - 1193:7, 1208:21</p> <p><b>tend</b> [1] - 1141:25</p> <p><b>term</b> [12] - 1010:10, 1054:12, 1055:12, 1056:12, 1143:5, 1165:23, 1166:1, 1166:4, 1166:17,</p>	<p>1226:22, 1226:23, 1245:8</p> <p><b>terms</b> [14] - 1059:22, 1061:7, 1076:19, 1092:1, 1121:9, 1121:10, 1121:19, 1122:12, 1122:17, 1132:7, 1185:4, 1223:11, 1226:18, 1248:25</p> <p><b>terrific</b> [1] - 1177:22</p> <p><b>territory</b> [1] - 1216:22</p> <p><b>test</b> [17] - 1065:7, 1077:8, 1077:9, 1077:10, 1077:11, 1081:11, 1081:15, 1081:18, 1081:21, 1083:9, 1117:19, 1117:20, 1118:17, 1119:6, 1131:15, 1138:2, 1142:4</p> <p><b>test-tube</b> [1] - 1131:15</p> <p><b>tested</b> [1] - 1173:12</p> <p><b>testified</b> [14] - 1055:7, 1087:10, 1114:6, 1119:25, 1126:13, 1138:25, 1154:12, 1162:8, 1162:22, 1188:19, 1207:15, 1215:22, 1217:4, 1218:25</p> <p><b>testify</b> [4] - 1120:16, 1146:8, 1186:24, 1217:6</p> <p><b>testifying</b> [2] - 1129:9, 1258:2</p> <p><b>testimony</b> [55] - 1015:9, 1015:25, 1017:3, 1017:7, 1017:8, 1024:22, 1025:15, 1086:17, 1090:19, 1101:13, 1110:2, 1110:9, 1110:15, 1125:12, 1129:4, 1130:12, 1158:15, 1165:23, 1175:14, 1182:13, 1183:18, 1187:1, 1188:21, 1189:1, 1189:3, 1193:14, 1193:22, 1199:2, 1202:13, 1213:20, 1216:2, 1219:5, 1223:4, 1223:8, 1229:20, 1231:11, 1237:7, 1237:14, 1238:11, 1238:20, 1238:22, 1239:1, 1239:22, 1245:11, 1258:4, 1258:9,</p>	<p>1259:24, 1260:3, 1261:4, 1261:10, 1262:4, 1264:6, 1264:14, 1264:22, 1265:5</p> <p><b>testing</b> [13] - 1033:15, 1036:10, 1039:10, 1093:20, 1093:22, 1117:21, 1118:4, 1118:9, 1118:14, 1118:15, 1119:9, 1148:8, 1148:13</p> <p><b>tests</b> [11] - 1033:20, 1076:16, 1081:4, 1082:1, 1082:8, 1083:10, 1083:11, 1083:14, 1084:11, 1093:25, 1178:23</p> <p><b>TEVA</b> [1] - 1:7</p> <p><b>Teva</b> [3] - 1005:6, 1023:1, 1260:3</p> <p><b>Teva's</b> [1] - 1260:20</p> <p><b>text</b> [3] - 1130:3, 1242:19, 1256:20</p> <p><b>TFH</b> [1] - 1251:21</p> <p><b>THE</b> [382] - 1:2, 1:3, 1006:5, 1014:2, 1014:10, 1014:12, 1014:18, 1014:21, 1015:1, 1015:11, 1017:6, 1017:17, 1018:3, 1018:7, 1018:11, 1018:15, 1018:19, 1018:22, 1019:1, 1019:5, 1019:8, 1019:12, 1019:14, 1019:16, 1020:4, 1020:5, 1020:21, 1020:24, 1023:8, 1023:11, 1023:12, 1023:15, 1023:16, 1024:4, 1024:10, 1024:15, 1024:21, 1025:2, 1025:5, 1026:7, 1028:11, 1032:20, 1033:25, 1034:2, 1034:11, 1035:2, 1035:20, 1035:22, 1037:2, 1038:14, 1044:9, 1047:8, 1047:11, 1048:25, 1052:6, 1054:6, 1054:8, 1054:11, 1054:18, 1055:10, 1055:24, 1056:6, 1056:17, 1057:5, 1057:11, 1058:1, 1058:3, 1058:10, 1058:13, 1071:23,</p>
<p style="text-align: center;"><b>T</b></p>				
<p><b>Table</b> [1] - 1156:12</p> <p><b>table</b> [1] - 1153:14</p> <p><b>tables</b> [1] - 1095:18</p> <p><b>tablet</b> [1] - 1176:10</p> <p><b>tabs</b> [1] - 1269:20</p> <p><b>tacking</b> [1] - 1123:21</p> <p><b>tad</b> [1] - 1205:10</p> <p><b>talks</b> [6] - 1007:7, 1017:22, 1191:4, 1191:25, 1198:4, 1235:8</p> <p><b>target</b> [6] - 1035:18, 1180:14, 1182:10, 1183:4, 1196:9, 1196:16</p> <p><b>Tasimelton</b> [1] - 1159:24</p> <p><b>tasimelton</b> [193] - 1006:22, 1006:25, 1007:9, 1008:19, 1008:23, 1009:2, 1010:2, 1010:10, 1010:15, 1010:19, 1010:25, 1011:6, 1011:10, 1013:3, 1013:6, 1015:15, 1017:9, 1017:12,</p>				

1079:22, 1079:25, 1080:4, 1080:6, 1080:12, 1086:18, 1086:20, 1086:24, 1087:3, 1087:15, 1087:22, 1088:7, 1088:15, 1089:4, 1089:22, 1095:10, 1095:16, 1095:23, 1099:15, 1099:19, 1110:22, 1110:24, 1112:13, 1112:19, 1113:4, 1116:4, 1117:16, 1117:23, 1117:25, 1118:2, 1118:3, 1118:5, 1118:10, 1118:19, 1119:4, 1119:10, 1119:11, 1119:12, 1119:23, 1120:2, 1120:3, 1120:4, 1120:6, 1120:7, 1120:17, 1120:20, 1120:23, 1121:2, 1121:6, 1121:10, 1121:13, 1122:7, 1122:9, 1122:18, 1122:24, 1123:4, 1123:10, 1123:13, 1123:25, 1124:9, 1124:20, 1124:25, 1125:14, 1126:1, 1126:3, 1126:7, 1126:10, 1127:19, 1128:25, 1130:12, 1130:20, 1136:13, 1137:11, 1137:17, 1137:19, 1138:21, 1138:23, 1138:24, 1139:1, 1139:2, 1139:23, 1142:15, 1142:18, 1151:6, 1154:20, 1155:4, 1157:3, 1157:8, 1157:12, 1158:2, 1158:12, 1158:16, 1159:18, 1161:23, 1162:5, 1162:7, 1162:9, 1162:10, 1162:11, 1162:12, 1162:13, 1162:14, 1162:16, 1162:18, 1163:4, 1165:12, 1165:13, 1169:12, 1170:2, 1171:25, 1172:2, 1172:5, 1176:21, 1176:23, 1176:25, 1177:1, 1178:14, 1178:17, 1178:18, 1178:21, 1178:22, 1179:4,	1179:8, 1179:9, 1179:18, 1179:20, 1179:21, 1180:1, 1180:3, 1185:22, 1185:24, 1188:11, 1190:16, 1205:8, 1205:13, 1205:15, 1205:20, 1205:24, 1206:5, 1206:8, 1206:11, 1206:14, 1206:19, 1206:22, 1206:25, 1207:11, 1209:16, 1210:4, 1210:6, 1210:7, 1211:16, 1214:12, 1215:1, 1215:4, 1215:5, 1215:7, 1215:8, 1215:10, 1215:11, 1215:13, 1215:17, 1215:23, 1216:5, 1216:9, 1216:12, 1216:17, 1219:12, 1221:14, 1221:17, 1221:20, 1221:25, 1222:4, 1222:6, 1222:10, 1222:15, 1222:18, 1222:21, 1223:1, 1223:4, 1223:17, 1224:17, 1224:24, 1225:6, 1225:9, 1225:14, 1225:18, 1225:25, 1226:8, 1226:14, 1226:17, 1227:1, 1227:4, 1227:6, 1227:9, 1227:17, 1227:23, 1228:1, 1228:6, 1228:11, 1228:16, 1228:19, 1229:12, 1229:15, 1230:1, 1230:10, 1230:17, 1230:24, 1232:5, 1233:11, 1233:24, 1235:9, 1235:12, 1236:10, 1236:21, 1236:24, 1237:4, 1237:21, 1238:7, 1238:14, 1238:19, 1238:23, 1239:6, 1239:15, 1239:19, 1240:3, 1240:12, 1240:17, 1241:21, 1242:2, 1242:6, 1242:10, 1242:15, 1243:4, 1243:19, 1243:24, 1244:4, 1244:7, 1244:13, 1245:1, 1245:6, 1245:22, 1246:1, 1246:13, 1246:15,	1246:18, 1246:22, 1247:6, 1247:24, 1248:3, 1248:6, 1248:13, 1249:4, 1249:7, 1249:15, 1250:3, 1250:5, 1250:11, 1250:14, 1250:18, 1250:23, 1253:13, 1253:15, 1253:20, 1253:22, 1253:25, 1254:4, 1254:8, 1254:15, 1254:25, 1257:7, 1257:24, 1258:19, 1258:23, 1259:4, 1259:24, 1260:8, 1260:20, 1261:1, 1261:6, 1261:15, 1261:18, 1261:22, 1261:24, 1262:9, 1262:17, 1262:22, 1263:7, 1263:21, 1264:4, 1264:8, 1264:11, 1264:23, 1265:3, 1265:15, 1265:22, 1266:10, 1266:13, 1266:15, 1266:20, 1267:4, 1267:8, 1267:17, 1268:6, 1268:10, 1268:15, 1269:2, 1269:6, 1270:12, 1271:2, 1271:6, 1271:13, 1271:20 <b>themselves</b> [3] - 1103:25, 1113:24, 1184:11 <b>then-stimulated</b> [1] - 1177:14 <b>theory</b> [1] - 1052:21 <b>therapeutic</b> [2] - 1135:16 <b>therapeutics</b> [3] - 1028:2, 1028:4, 1187:22 <b>thereby</b> [1] - 1140:10 <b>therefore</b> [8] - 1016:10, 1024:21, 1051:8, 1108:1, 1176:5, 1244:23, 1259:19, 1260:6 <b>they've</b> [6] - 1073:5, 1114:8, 1122:5, 1185:1, 1231:10, 1247:9 <b>thinking</b> [4] - 1113:11, 1187:15, 1245:15, 1265:23 <b>third</b> [3] - 1031:15, 1098:3, 1120:13	<b>thirds</b> [1] - 1218:7 <b>thoughts</b> [1] - 1257:12 <b>thousand</b> [1] - 1219:20 <b>three</b> [13] - 1042:14, 1047:6, 1047:13, 1047:15, 1057:3, 1067:6, 1072:8, 1132:25, 1138:4, 1186:15, 1208:20, 1266:1, 1266:11 <b>threshold</b> [3] - 1010:6, 1010:18, 1010:24 <b>thresholds</b> [1] - 1011:11 <b>throughout</b> [5] - 1202:22, 1221:3, 1240:22, 1241:2, 1241:16 <b>Thursday</b> [4] - 1:16, 1267:21, 1269:8 <b>tie</b> [1] - 1248:24 <b>timely</b> [1] - 1016:7 <b>timing</b> [6] - 1167:3, 1180:10, 1180:16, 1181:24, 1200:5, 1200:15 <b>tired</b> [1] - 1025:6 <b>tissues</b> [1] - 1096:11 <b>title</b> [5] - 1013:1, 1072:3, 1099:22, 1136:16, 1160:1 <b>today</b> [15] - 1043:5, 1084:3, 1089:13, 1089:14, 1121:5, 1129:4, 1129:9, 1175:7, 1193:5, 1193:22, 1210:12, 1213:20, 1258:7, 1267:16, 1270:9 <b>together</b> [20] - 1011:5, 1029:9, 1033:12, 1041:5, 1042:1, 1044:20, 1046:2, 1048:15, 1053:22, 1104:21, 1191:23, 1225:5, 1241:17, 1241:21, 1241:22, 1242:16, 1254:20, 1262:24, 1263:8, 1265:16 <b>Tokyo</b> [1] - 1165:6 <b>tomorrow</b> [2] - 1257:6, 1267:17 <b>took</b> [5] - 1106:10, 1125:1, 1210:15, 1210:16, 1259:21 <b>top</b> [23] - 1007:20, 1008:6, 1008:16, 1044:21, 1046:11,	1061:21, 1071:25, 1094:12, 1095:8, 1096:2, 1107:14, 1113:15, 1114:14, 1114:15, 1129:25, 1130:3, 1131:5, 1132:25, 1143:14, 1153:14, 1235:20, 1239:18, 1253:1 <b>topic</b> [4] - 1036:16, 1102:14, 1106:12, 1218:20 <b>total</b> [8] - 1124:12, 1124:14, 1157:21, 1207:3, 1207:7, 1266:11, 1268:24 <b>totality</b> [2] - 1104:8, 1193:18 <b>totally</b> [3] - 1098:17, 1113:12, 1258:23 <b>touch</b> [3] - 1212:19, 1250:1, 1250:9 <b>touched</b> [2] - 1016:12, 1222:1 <b>touches</b> [1] - 1250:7 <b>touching</b> [2] - 1231:6, 1252:14 <b>tough</b> [1] - 1245:16 <b>toxic</b> [1] - 1079:6 <b>toxicities</b> [1] - 1026:24 <b>toxicity</b> [2] - 1041:15, 1047:18 <b>toxicology</b> [1] - 1127:24 <b>tract</b> [2] - 1030:21, 1051:18 <b>trained</b> [1] - 1026:14 <b>training</b> [1] - 1163:19 <b>Transcript</b> [1] - 1:16 <b>transcript</b> [9] - 1023:21, 1088:13, 1089:19, 1158:8, 1219:2, 1219:4, 1270:3, 1271:1, 1272:5 <b>transcripts</b> [2] - 1269:24, 1269:25 <b>transfected</b> [1] - 1066:4 <b>transfection</b> [1] - 1065:17 <b>transformed</b> [1] - 1187:24 <b>transition</b> [1] - 1180:21 <b>travel</b> [1] - 1165:4 <b>treat</b> [13] - 1037:8, 1057:17, 1059:23, 1174:2, 1186:6,
--	--	--	--	--

<p>1186:12, 1195:6, 1210:13, 1211:7, 1220:2, 1222:12, 1222:22, 1224:13 <b>treated</b> [10] - 1049:8, 1050:24, 1194:5, 1196:24, 1197:6, 1212:16, 1214:17, 1214:18, 1214:19, 1218:1 <b>treating</b> [18] - 1042:4, 1057:19, 1118:24, 1191:8, 1192:1, 1192:3, 1192:6, 1192:8, 1192:15, 1193:15, 1194:16, 1195:2, 1195:15, 1196:15, 1198:3, 1198:4, 1210:20, 1210:21 <b>treatment</b> [34] - 1049:9, 1051:1, 1062:5, 1091:18, 1164:1, 1186:17, 1192:11, 1192:19, 1192:21, 1193:10, 1193:20, 1193:21, 1193:23, 1193:25, 1194:2, 1194:7, 1194:10, 1194:19, 1195:24, 1201:1, 1207:20, 1209:23, 1210:16, 1211:22, 1217:8, 1217:22, 1220:9, 1222:6, 1222:12, 1223:5, 1223:16, 1223:19 <b>treats</b> [2] - 1109:25, 1110:1 <b>tree</b> [4] - 1096:3, 1098:4, 1098:7, 1098:11 <b>tremendous</b> [2] - 1203:11, 1263:2 <b>trial</b> [27] - 1006:3, 1017:19, 1017:21, 1020:22, 1087:4, 1117:16, 1118:18, 1164:8, 1165:23, 1166:25, 1182:14, 1182:24, 1184:3, 1186:13, 1186:16, 1194:3, 1198:22, 1203:22, 1208:21, 1210:19, 1226:6, 1228:23, 1262:8, 1266:23, 1267:1, 1271:18, 1271:23 <b>Trial</b> [1] - 1:16 <b>trials</b> [9] - 1059:20,</p>	<p>1178:13, 1198:17, 1198:19, 1208:19, 1211:25, 1216:20, 1216:23, 1262:13 <b>tried</b> [10] - 1011:7, 1014:5, 1187:17, 1187:18, 1193:5, 1211:7, 1214:21, 1232:13, 1268:13, 1271:23 <b>trigger</b> [1] - 1143:17 <b>tripped</b> [1] - 1197:24 <b>true</b> [12] - 1011:8, 1082:6, 1082:13, 1082:14, 1083:25, 1084:4, 1084:5, 1091:10, 1118:19, 1171:2, 1202:2, 1272:4 <b>trusting</b> [1] - 1079:18 <b>try</b> [21] - 1011:14, 1068:16, 1084:23, 1085:3, 1105:25, 1108:24, 1143:22, 1165:6, 1165:7, 1166:9, 1166:21, 1166:22, 1167:2, 1168:12, 1175:13, 1186:3, 1187:20, 1199:9, 1199:11, 1200:12, 1214:22 <b>trying</b> [28] - 1011:9, 1012:24, 1053:9, 1058:7, 1059:23, 1060:4, 1060:13, 1061:8, 1077:12, 1098:18, 1105:25, 1135:8, 1158:3, 1165:5, 1166:23, 1167:4, 1192:13, 1194:14, 1194:15, 1195:13, 1203:17, 1223:11, 1224:4, 1229:22, 1240:16, 1244:20, 1245:17, 1262:12 <b>tube</b> [3] - 1131:15, 1138:2, 1142:4 <b>tubercular</b> [2] - 1154:2, 1154:8 <b>Tufts</b> [1] - 1025:21 <b>TUNNELL</b> [1] - 1005:12 <b>turn</b> [47] - 1008:18, 1025:24, 1028:21, 1029:5, 1033:23, 1034:13, 1035:5, 1036:1, 1036:17, 1037:15, 1037:19, 1038:23, 1039:17,</p>	<p>1040:25, 1042:8, 1046:4, 1048:10, 1063:7, 1063:8, 1068:21, 1069:19, 1082:17, 1086:8, 1094:3, 1094:25, 1101:17, 1102:2, 1114:2, 1114:11, 1115:3, 1117:20, 1118:13, 1127:12, 1129:18, 1130:21, 1134:22, 1136:3, 1136:25, 1144:4, 1150:17, 1160:2, 1165:13, 1169:15, 1171:12, 1174:8, 1174:24 <b>turned</b> [2] - 1059:9, 1175:1 <b>turning</b> [20] - 1027:5, 1027:24, 1028:13, 1030:5, 1031:7, 1031:18, 1032:23, 1033:23, 1040:6, 1043:18, 1045:24, 1047:6, 1047:23, 1049:3, 1050:20, 1068:22, 1071:15, 1189:13, 1236:15, 1267:5 <b>turns</b> [3] - 1065:25, 1229:10, 1237:25 <b>twice</b> [2] - 1120:5, 1173:9 <b>two</b> [80] - 1006:18, 1007:15, 1007:22, 1009:4, 1009:6, 1009:20, 1016:16, 1026:18, 1028:22, 1029:7, 1035:12, 1040:14, 1040:20, 1041:4, 1041:10, 1048:15, 1056:22, 1063:9, 1074:21, 1081:4, 1081:23, 1083:4, 1083:9, 1083:11, 1083:14, 1083:15, 1084:4, 1085:21, 1086:1, 1086:5, 1089:9, 1090:23, 1090:24, 1095:9, 1097:1, 1108:16, 1110:15, 1110:17, 1116:15, 1125:11, 1130:2, 1132:13, 1135:4, 1137:25, 1144:19, 1148:2, 1148:9, 1155:12, 1157:16, 1158:9, 1161:24,</p>	<p>1163:21, 1169:16, 1172:19, 1173:7, 1175:6, 1178:8, 1181:25, 1188:15, 1195:10, 1196:19, 1201:16, 1202:9, 1217:19, 1217:20, 1218:7, 1220:23, 1231:15, 1231:21, 1241:4, 1241:10, 1251:9, 1252:8, 1255:8, 1255:11, 1263:9, 1266:24, 1266:25, 1269:24 <b>two-column</b> [1] - 1063:9 <b>two-hour</b> [1] - 1175:6 <b>two-minute</b> [1] - 1125:11 <b>two-page</b> [1] - 1263:9 <b>two-process</b> [1] - 1220:23 <b>two-thirds</b> [1] - 1218:7 <b>two-year</b> [1] - 1026:18 <b>twofold</b> [1] - 1045:19 <b>Tylenol</b> [3] - 1139:14, 1139:16 <b>type</b> [5] - 1039:10, 1128:8, 1134:8, 1141:19, 1229:5 <b>types</b> [4] - 1148:16, 1167:15, 1229:7 <b>typical</b> [1] - 1141:19 <b>typically</b> [2] - 1088:15, 1145:14</p>	<p>1098:11, 1121:3, 1125:22, 1126:13, 1127:22, 1139:11, 1150:3, 1193:2, 1215:24, 1218:5, 1221:7, 1233:6, 1233:7, 1259:14 <b>underestimate</b> [1] - 1141:22 <b>underlying</b> [1] - 1103:16 <b>understood</b> [4] - 1012:5, 1065:15, 1207:9, 1234:5 <b>undesirable</b> [1] - 1253:24 <b>undisputed</b> [3] - 1024:17, 1113:2, 1234:14 <b>unduly</b> [1] - 1195:13 <b>unexpected</b> [2] - 1015:25, 1184:5 <b>unfortunately</b> [4] - 1167:4, 1185:2, 1202:19, 1245:24 <b>uninduced</b> [1] - 1116:20 <b>unique</b> [2] - 1032:1, 1142:1 <b>UNITED</b> [1] - 1:2 <b>United</b> [5] - 1059:13, 1059:25, 1185:14, 1212:4, 1219:22 <b>universe</b> [2] - 1101:25, 1102:13 <b>University</b> [3] - 1025:22, 1126:20, 1127:24 <b>unless</b> [3] - 1158:7, 1248:16, 1249:5 <b>unlike</b> [2] - 1174:23, 1226:6 <b>unlikely</b> [2] - 1116:15, 1141:22 <b>unmet</b> [2] - 1119:18, 1186:7 <b>unnecessary</b> [1] - 1102:3 <b>unpublished</b> [1] - 1251:23 <b>unreliability</b> [1] - 1264:15 <b>unsure</b> [1] - 1124:18 <b>unusual</b> [1] - 1170:24 <b>up</b> [98] - 1006:15, 1007:6, 1010:1, 1010:6, 1011:5, 1011:12, 1012:24, 1014:16, 1016:19, 1020:1, 1024:10,</p>
<b>U</b>				
<p><b>U.S</b> [1] - 1272:7 <b>ultimate</b> [1] - 1021:7 <b>ultimately</b> [4] - 1030:23, 1119:8, 1247:11, 1247:18 <b>unable</b> [1] - 1060:21 <b>unaffected</b> [6] - 1067:2, 1067:5, 1068:1, 1068:18, 1071:4, 1074:10 <b>unambiguous</b> [3] - 1251:25, 1252:23, 1255:12 <b>unchanged</b> [2] - 1133:3, 1241:9 <b>unclear</b> [1] - 1194:12 <b>uncontested</b> [1] - 1271:11 <b>under</b> [21] - 1006:6, 1020:3, 1020:4, 1054:12, 1057:4, 1087:12, 1087:24,</p>				



1025:18, 1026:10, 1027:8, 1031:16, 1033:4, 1033:9, 1034:4, 1034:5, 1036:7, 1039:18, 1045:3, 1054:20, 1061:16, 1061:20, 1063:24, 1065:3, 1069:5, 1071:25, 1073:18, 1078:2, 1080:15, 1092:18, 1095:7, 1096:19, 1106:19, 1107:9, 1109:18, 1113:13, 1113:14, 1114:13, 1114:15, 1115:6, 1117:19, 1118:10, 1119:2, 1124:3, 1129:6, 1129:22, 1132:20, 1137:21, 1140:4, 1140:18, 1141:3, 1144:19, 1147:15, 1149:9, 1154:13, 1154:19, 1156:12, 1159:16, 1165:10, 1165:13, 1166:10, 1168:1, 1168:2, 1168:3, 1168:10, 1168:11, 1172:3, 1186:24, 1187:1, 1187:8, 1191:11, 1191:21, 1194:8, 1197:24, 1199:7, 1199:10, 1204:25, 1220:18, 1225:11, 1226:9, 1226:25, 1232:2, 1233:1, 1234:14, 1235:1, 1249:11, 1255:1, 1258:11, 1261:4, 1264:16, 1270:13 <b>update</b> [1] - 1122:21 <b>upheld</b> [1] - 1246:19 <b>uponti</b> [1] - 1038:9 <b>upregulated</b> [1] - 1093:16 <b>urine</b> [6] - 1076:1, 1077:24, 1133:4, 1134:13, 1195:10, 1196:18 <b>USA</b> [1] - 1:7 <b>useful</b> [3] - 1225:5, 1258:21, 1259:2 <b>usual</b> [8] - 1045:21, 1168:12, 1172:18, 1172:20, 1176:7, 1179:13, 1203:2, 1203:7 <b>utility</b> [4] - 1259:20,	1263:18, 1263:19 <b>utterance</b> [1] - 1056:2  <b>V</b>  <b>VA</b> [6] - 1219:15, 1219:17, 1220:5, 1220:8, 1220:18, 1221:9 <b>Vachharajani</b> [46] - 1071:7, 1071:12, 1071:18, 1072:1, 1072:16, 1072:20, 1073:8, 1073:17, 1081:11, 1092:18, 1092:19, 1092:23, 1093:1, 1100:7, 1103:16, 1103:21, 1104:23, 1105:1, 1105:2, 1105:9, 1112:4, 1112:9, 1112:11, 1112:15, 1113:2, 1113:17, 1116:9, 1128:6, 1128:9, 1129:18, 1130:5, 1130:9, 1130:11, 1131:1, 1131:10, 1131:13, 1131:22, 1140:21, 1140:23, 1141:6, 1141:15, 1142:9, 1160:21, 1178:2, 1180:1 <b>VACHHARAJANI</b> [1] - 1071:8 <b>validity</b> [6] - 1011:18, 1011:19, 1223:21, 1265:8, 1266:6, 1266:7 <b>value</b> [5] - 1214:1, 1214:5, 1214:7, 1257:17, 1259:18 <b>Van</b> [1] - 1044:1 <b>VANDA</b> [1] - 1:5 <b>Vanda</b> [22] - 1005:13, 1009:7, 1010:1, 1010:2, 1010:6, 1160:6, 1194:3, 1195:12, 1211:7, 1212:20, 1212:22, 1213:3, 1213:5, 1213:6, 1213:13, 1213:23, 1214:4, 1214:5, 1215:5, 1215:10, 1249:18, 1260:16 <b>Vanda's</b> [2] - 1120:18, 1162:19 <b>variability</b> [1] - 1090:15	<b>variables</b> [1] - 1233:20 <b>varieties</b> [1] - 1031:18 <b>variety</b> [1] - 1139:11 <b>various</b> [3] - 1042:13, 1082:6, 1184:6 <b>vast</b> [1] - 1148:17 <b>verb</b> [2] - 1067:2, 1240:24 <b>verified</b> [1] - 1141:16 <b>version</b> [1] - 1271:14 <b>versus</b> [5] - 1082:10, 1086:22, 1117:18, 1251:21, 1252:21 <b>via</b> [1] - 1110:3 <b>victim</b> [2] - 1041:8, 1045:18 <b>view</b> [18] - 1009:23, 1057:3, 1102:4, 1103:20, 1104:5, 1113:7, 1197:17, 1224:12, 1231:18, 1235:3, 1235:24, 1236:8, 1243:21, 1244:8, 1244:21, 1245:4, 1250:10, 1257:14 <b>vis-à-vis</b> [1] - 1081:25 <b>vitae</b> [2] - 1127:15, 1169:7 <b>Vitro</b> [2] - 1115:8, 1115:14 <b>vitro</b> [64] - 1033:1, 1033:14, 1036:10, 1039:12, 1039:23, 1046:20, 1076:19, 1076:22, 1076:23, 1077:2, 1077:13, 1081:5, 1081:18, 1081:25, 1082:7, 1083:5, 1084:12, 1084:14, 1085:14, 1092:20, 1093:20, 1096:10, 1097:2, 1098:15, 1098:16, 1098:19, 1099:22, 1100:7, 1100:11, 1101:1, 1101:10, 1103:22, 1107:12, 1114:17, 1115:21, 1117:18, 1117:19, 1117:20, 1117:25, 1118:3, 1118:12, 1118:14, 1118:17, 1118:23, 1119:6, 1119:12, 1128:8, 1135:22, 1135:24, 1136:7, 1136:19, 1138:1, 1138:8, 1138:17, 1139:14, 1142:11, 1145:15,	1150:6, 1152:20, 1153:4, 1159:2, 1159:7, 1160:11, 1161:1 <b>vivo</b> [35] - 1046:20, 1046:21, 1050:15, 1076:20, 1077:6, 1077:8, 1077:9, 1077:11, 1077:13, 1077:14, 1084:11, 1084:13, 1084:17, 1086:2, 1092:4, 1092:9, 1093:5, 1093:9, 1093:15, 1093:18, 1098:15, 1098:21, 1100:24, 1101:18, 1117:18, 1117:21, 1118:1, 1118:4, 1118:13, 1118:15, 1119:8, 1139:6, 1143:17, 1150:6, 1159:8 <b>vocabulary</b> [3] - 1058:17, 1064:23, 1076:18 <b>voice</b> [1] - 1165:10 <b>volunteers</b> [1] - 1106:4  <b>W</b>  <b>wait</b> [5] - 1033:25, 1058:13, 1176:21, 1192:22, 1246:13 <b>waited</b> [1] - 1068:9 <b>waiting</b> [1] - 1122:21 <b>waiver</b> [1] - 1226:7 <b>Wake</b> [1] - 1192:4 <b>wake</b> [23] - 1167:21, 1168:2, 1168:6, 1168:10, 1170:24, 1179:6, 1179:11, 1184:1, 1191:5, 1191:9, 1192:15, 1192:17, 1194:17, 1196:9, 1196:13, 1197:10, 1203:6, 1203:11, 1203:16, 1203:19, 1220:7, 1220:10 <b>wakening</b> [1] - 1202:23 <b>wakes</b> [1] - 1168:3 <b>walk</b> [1] - 1030:9 <b>wants</b> [4] - 1210:8, 1224:2, 1228:3, 1257:16 <b>War</b> [1] - 1054:23 <b>warn</b> [2] - 1080:1, 1268:10	<b>warned</b> [1] - 1100:22 <b>warning</b> [4] - 1046:3, 1100:18, 1100:23, 1102:22 <b>warnings</b> [2] - 1049:21, 1100:16 <b>warns</b> [1] - 1067:10 <b>warranted</b> [1] - 1091:18 <b>watch</b> [1] - 1104:22 <b>watching</b> [1] - 1258:8 <b>ways</b> [1] - 1231:23 <b>weak</b> [2] - 1237:11, 1237:12 <b>Wednesday</b> [1] - 1271:4 <b>week</b> [5] - 1166:25, 1266:23, 1268:23, 1269:15, 1271:4 <b>weekend</b> [2] - 1267:14, 1267:20 <b>weeks</b> [4] - 1195:11, 1196:19, 1257:19, 1265:11 <b>weigh</b> [1] - 1245:16 <b>weight</b> [1] - 1187:22 <b>weight-promoting</b> [1] - 1187:22 <b>Weir</b> [27] - 1061:16, 1063:24, 1064:15, 1069:4, 1071:25, 1073:14, 1079:18, 1095:1, 1096:18, 1096:19, 1099:7, 1106:19, 1113:14, 1114:13, 1115:3, 1115:5, 1129:2, 1129:6, 1129:22, 1130:21, 1132:20, 1134:22, 1137:20, 1140:4, 1140:17, 1141:2, 1166:12 <b>WEISS</b> [1] - 1005:8 <b>welcome</b> [1] - 1217:1 <b>well-aligned</b> [1] - 1239:24 <b>WELLS</b> [1] - 1005:4 <b>Westlaw</b> [1] - 1233:22 <b>WHARTON</b> [1] - 1005:8 <b>wheel</b> [1] - 1260:7 <b>whereas</b> [2] - 1237:16, 1244:18 <b>wherein</b> [2] - 1236:4, 1236:6 <b>white</b> [3] - 1063:7, 1126:16, 1169:1 <b>whole</b> [12] - 1075:7, 1096:8, 1100:21, 1107:6, 1182:17,
---	---	---	---	---

<p>1183:2, 1246:23, 1248:14, 1251:13, 1259:16, 1263:4, 1267:14</p> <p><b>wide</b> [1] - 1165:18</p> <p><b>WILLIAM</b> [1] - 1005:5</p> <p><b>Williams</b> [1] - 1052:15</p> <p><b>Wilmington</b> [4] - 1:15, 1054:22, 1068:8, 1165:5</p> <p><b>window</b> [1] - 1203:7</p> <p><b>wisdom</b> [1] - 1174:1</p> <p><b>wise</b> [1] - 1124:3</p> <p><b>wiser</b> [1] - 1226:4</p> <p><b>wishing</b> [1] - 1253:9</p> <p><b>withdraw</b> [3] - 1091:7, 1092:16</p> <p><b>withdrawn</b> [9] - 1059:11, 1060:24, 1061:8, 1067:16, 1072:14, 1078:4, 1092:16, 1103:5, 1109:19</p> <p><b>WITNESS</b> [41] - 1020:5, 1020:24, 1023:11, 1023:15, 1034:2, 1035:22, 1080:4, 1095:10, 1117:23, 1118:2, 1118:5, 1118:19, 1119:10, 1119:12, 1120:2, 1120:4, 1120:7, 1137:19, 1138:23, 1139:1, 1159:18, 1162:9, 1162:11, 1162:13, 1162:16, 1165:12, 1176:23, 1177:1, 1178:17, 1178:21, 1179:4, 1179:9, 1179:20, 1180:1, 1185:24, 1188:11, 1210:6, 1215:4, 1215:7, 1215:10, 1215:13</p> <p><b>witness</b> [38] - 1014:1, 1018:1, 1018:2, 1020:2, 1024:6, 1052:3, 1056:13, 1057:21, 1087:4, 1087:5, 1087:6, 1087:7, 1087:8, 1087:11, 1087:12, 1087:23, 1087:25, 1095:15, 1113:10, 1120:14, 1120:18, 1123:1, 1123:2, 1123:5, 1123:8, 1124:1, 1124:6, 1126:12, 1162:8,</p>	<p>1162:19, 1162:22, 1165:9, 1206:10, 1206:19, 1207:7, 1214:11, 1220:15</p> <p><b>Witness</b> [4] - 1014:13, 1120:8, 1162:17, 1215:14</p> <p><b>witnesses</b> [7] - 1016:20, 1121:4, 1124:6, 1125:13, 1231:5, 1258:8, 1265:10</p> <p><b>Women's</b> [1] - 1163:10</p> <p><b>wonder</b> [2] - 1054:24, 1270:23</p> <p><b>wondering</b> [4] - 1007:18, 1014:15, 1019:10, 1223:11</p> <p><b>Word</b> [1] - 1271:14</p> <p><b>word</b> [23] - 1055:19, 1062:24, 1068:4, 1070:17, 1078:2, 1115:17, 1192:7, 1192:15, 1193:13, 1196:22, 1229:10, 1237:25, 1241:13, 1246:10, 1247:3, 1247:4, 1248:1, 1249:19, 1250:16, 1252:12, 1255:6, 1267:24</p> <p><b>wording</b> [2] - 1102:24, 1103:2</p> <p><b>words</b> [19] - 1054:2, 1064:19, 1071:6, 1073:2, 1074:16, 1074:18, 1118:16, 1179:1, 1230:2, 1231:9, 1235:8, 1239:4, 1241:5, 1241:16, 1246:23, 1247:13, 1252:1, 1256:15, 1256:16</p> <p><b>workers</b> [1] - 1166:21</p> <p><b>works</b> [1] - 1262:24</p> <p><b>world</b> [6] - 1083:15, 1094:18, 1139:5, 1165:18, 1245:4, 1250:10</p> <p><b>worry</b> [3] - 1041:14, 1041:22, 1154:25</p> <p><b>worse</b> [2] - 1186:22, 1249:2</p> <p><b>worst</b> [1] - 1185:3</p> <p><b>wrapped</b> [1] - 1124:3</p> <p><b>write</b> [5] - 1203:21, 1203:22, 1232:12, 1266:25, 1267:2</p> <p><b>writing</b> [1] - 1270:8</p>	<p><b>written</b> [25] - 1038:8, 1098:14, 1133:14, 1183:2, 1232:8, 1232:24, 1234:7, 1235:6, 1235:7, 1235:25, 1236:9, 1237:17, 1238:5, 1242:3, 1242:22, 1244:21, 1244:25, 1251:8, 1251:14, 1253:7, 1253:8, 1253:11, 1253:16, 1270:7, 1270:13</p> <p><b>wrote</b> [3] - 1099:10, 1099:22, 1232:5</p>	<p><b>yourself</b> [10] - 1013:14, 1013:20, 1017:17, 1057:7, 1082:25, 1086:9, 1088:1, 1128:13, 1163:6, 1212:17</p>
			<b>Z</b>
			<p><b>zolpidem</b> [1] - 1030:1</p> <p><b>zone</b> [2] - 1203:6, 1203:19</p> <p><b>zoom</b> [4] - 1064:2, 1064:15, 1075:5, 1095:8</p> <p><b>zooming</b> [1] - 1135:21</p>
		<b>X</b>	
		<p><b>Xanax</b> [1] - 1029:22</p> <p><b>XenoTech</b> [2] - 1126:25, 1128:11</p> <p><b>XPD</b> [3] - 1126:21, 1126:23, 1127:1</p>	
		<b>Y</b>	
		<p><b>year</b> [7] - 1026:15, 1026:16, 1026:18, 1120:5, 1213:11, 1261:1, 1268:11</p> <p><b>years</b> [11] - 1027:4, 1027:13, 1030:4, 1120:5, 1163:21, 1164:17, 1186:11, 1244:22, 1259:21, 1260:23, 1261:5</p> <p><b>yellow</b> [5] - 1030:11, 1031:22, 1049:7, 1050:23, 1087:8</p> <p><b>yes/no</b> [1] - 1141:12</p> <p><b>yesterday</b> [16] - 1006:11, 1009:14, 1014:6, 1017:7, 1057:21, 1068:8, 1121:14, 1121:17, 1174:9, 1174:23, 1175:4, 1175:14, 1205:23, 1208:19, 1218:13, 1229:11</p> <p><b>yesterday's</b> [2] - 1123:20, 1183:17</p> <p><b>York</b> [2] - 1054:22, 1165:20</p> <p><b>young</b> [2] - 1261:11, 1261:13</p> <p><b>YOUNG</b> [9] - 1005:9, 1014:3, 1019:17, 1019:19, 1019:25, 1020:6, 1021:1, 1023:7, 1037:4</p>	